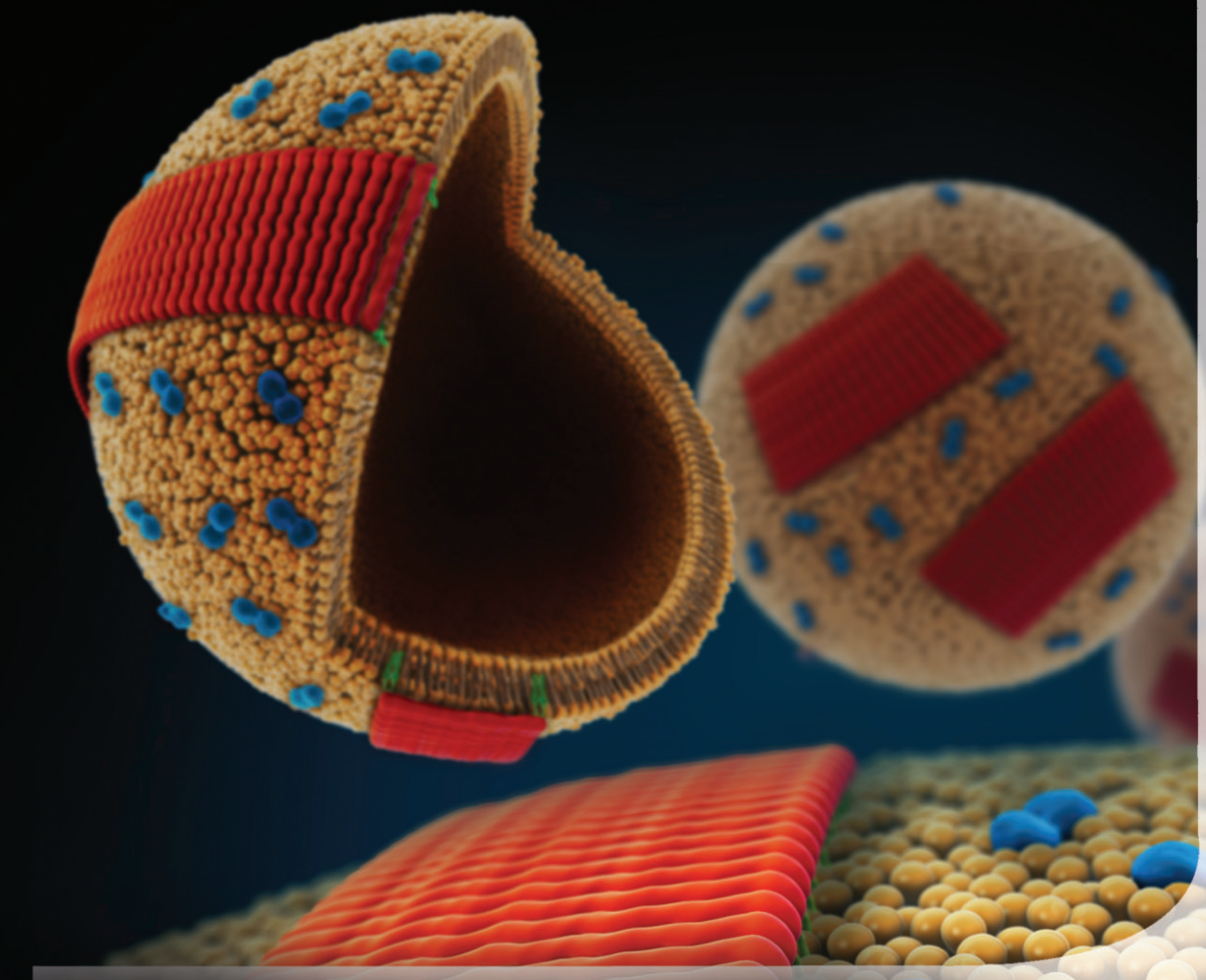
Drug Development & Delivery

October 2020 Vol 20 No 7 www.drug-dev.com

Targeting Misfolded Proteins



The Science & Business of Pharmaceutical and Biological Drug Development

Steven Gross, MS
How Custom Assay Development Helped Spur Precision Medicine Research in Multiple Myeloma

Andrea Pfeifer, PhD
Morphomer™ & SupraAntigen™ Platforms: Targeting Misfolded Proteins in Neurodegenerative Disorders

Vinod Patil, PhD
Dissolving Bioavailability & Solubility Challenges in Formulation & Development

IN THIS ISSUE

INTERVIEW WITH ENTERIS BIOPHARMA'S CEO
RAJIV KHOSLA, PHD

PEGYLATION 24
Esay Okutgen, PhD
Alper Orhan, MSc
Josef Bossart, PhD

STREAMLINING MANUFACTURING 34
Dustin Campbell

TRANSDERMAL DELIVERY 38
Sally Waterman, PhD
Vasiliki Nikolaou, PhD

INHALTION DEVICES 46
Andreas Meliniotis

OVER-ENCAPSULATION CAPSULES 50
Julien Lamps

IMMUNOGENICITY TESTING 66
Leon Shi, PhD
Lan Li, MS
Jing Shi, PhD

GATTEFOSSÉ

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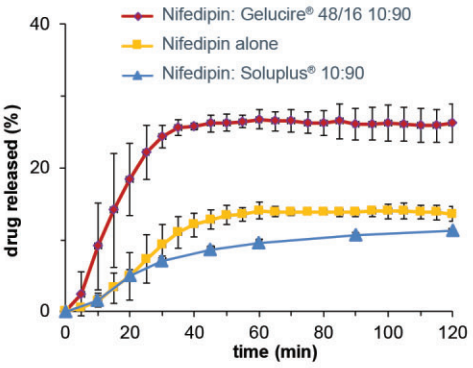
Depending on the choice of excipient and process, these excipients may serve as plasticizers, and carriers for a wide range of API.



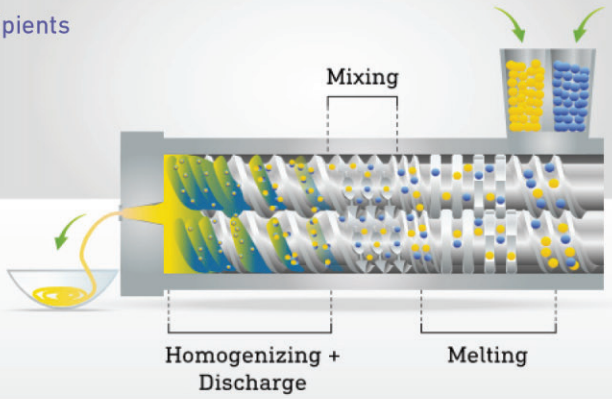
Drug release from Nifedipine milled extrudates filled into hard gelatin capsules

Contact Us

We help clients in various stages of drug development, beginning with drug solubility screening in solid lipid excipients, evaluating stability and compatibility with the API, and the characterization of the drug delivery system.

Melt extrusion with lipid excipients

Gelucire® 48/16
Extrudate



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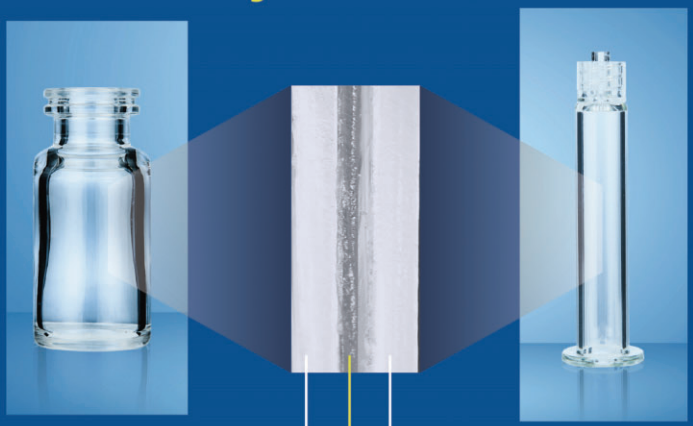
OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



Water Vapor Barrier Layer (COP)

Oxygen Barrier Layer (New Polymer)

Drug Contact Layer (COP)

- Excellent Oxygen Barrier
- High Water Vapor Barrier
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- For Biologics & Regenerative Medicine

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Mitsubishi Gas Chemical America, Inc.

http://www.mgc-a.com

E-mail: nb3.pharmapackage@mgc.co.jp

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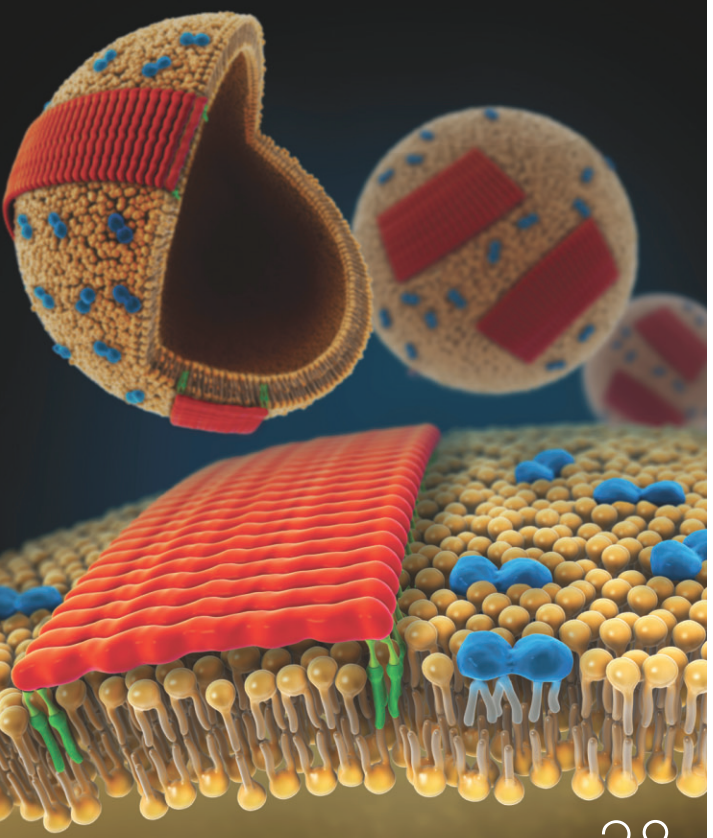
Morphomer™ & SupraAntigen™ Platforms

"The pipeline is powered by the company's two proprietary drug development platforms, SupraAntigen™ and Morphomer™. Together, these platforms accelerate the design, development, and validation of highly selective small molecules, antibodies, and vaccines for therapeutic and diagnostic applications. These platforms are complementary and have been optimized specifically to overcome the challenges of developing therapeutic or diagnostic candidates for CNS proteinopathies."



p.28

Table of Contents

Assay Development

18 **Case Study: How Custom Assay Development Helped Spur Precision Medicine Research in Multiple Myeloma**

Steven Gross, MS, provides a behind-the-scenes look at the CMMC assay development process (from 2010 through today) to show how pharmaceutical companies can effectively partner with a laboratory to design customized assays that complement their drug discovery and development programs.

Pegylation

24 **PEGylation - Three Decades of Product Approvals & Technology Development**

Esay Okutgen, PhD, Alper Orhan, MSc, and Josef Bossart, PhD, believe with the 30-year anniversary of the first product approval using PEG (polyethylene oxide polymer) conjugation, it seems an appropriate occasion to review the evolution of the technology (PEGylation) and subsequent product approvals.

Platform Technology

28 **Morphomer™ & SupraAntigen™ Platforms: Targeting Misfolded Proteins in Neurodegenerative Disorders**

Andrea Pfeifer, PhD, details the efforts to develop the therapeutic and diagnostic tools necessary to enable precision medicine approaches targeting the right protein, at the right time, in the right patient.

CDMO Case Study

34 **AJILITY: Streamlining Drug Product Manufacturing**

Dustin Campbell says the AJILITY platform takes the burden off clients and allows his company to drive, manage, and support their drug product manufacturing, maximizing speed and success, while prioritizing these programs are driven to completion.

Drug Delivery

38 **Recognizing the Patient Potential for Transdermal Drug Delivery**

Sally Waterman, PhD, and Vasiliki Nikolaou, PhD, explain how transdermal drug delivery patches have the potential to significantly improve not only the outcome of treatments, but also the quality of life for those patients using them.

Executive Interview

42 **Immunic Therapeutics: Developing Next-Generation Oral Drugs in Chronic Inflammatory, Autoimmune & Infectious Diseases**

Daniel Vitt, PhD, Immunic's Chief Executive Officer and President, discusses his company's pipeline of selective, small molecule therapies aimed at treating chronic inflammatory and autoimmune diseases, and its recent progress.

ADARE PHARMACEUTICALS IS NOW ADARE PHARMA SOLUTIONS

DIFFERENT NAME. SAME CUSTOMER FOCUS.

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Inhalation Devices

"The device development process typically follows a stage-gate process in which the project is reviewed with a board of representatives from across the relevant disciplines. The development is structured so that initially, the Target Product Profile (TPP), user requirements, including the user needs and intended uses, are reviewed at the first stage-gate, followed by the concepts at the second stage-gate, formal designs, device verification, manufacturing equipment, validation, and finally preparation for market."

p.46

Table of Contents

Device Development

46 Designing Devices for Inhaled Drugs

Andreas Meliniotis explains how there is plenty of opportunity for the development of new, improved devices to ensure inhaled drugs can be accessible for a wide range of patients and can treat various diseases and conditions effectively.

Over-Encapsulation Capsules

50 Double-Blind, Zero Bias: Over-Encapsulation – The Right Tool for Blinding Studies?

Julien Lamps believes that while many blinding options are available to drug sponsors and external clinical research partners, over-encapsulation remains a popular choice for its dosing simplicity, trial efficacy, patient accessibility, and cost-effectiveness.

Executive Interview

54 Enteris BioPharma: Pioneers in Oral Formulation Development

Dr. Rajiv Khosla, CEO of Enteris BioPharma, discusses how his company's innovative oral formulation technology is helping the pharmaceutical industry overcome the hurdle of low bioavailability to reshape treatment categories and expand market opportunities with minimal financial and regulatory risks.

OSD Formulations

58 Dissolving Bioavailability & Solubility Challenges in Formulation & Development

Vinod Patil, PhD, says many of the innovative and novel formulations introduced throughout the past decade have had to cope with poorly water-soluble APIs. Considering the pace of development, overcoming solubility issues will remain problematic, and this is especially true for important new classes of pharmaceuticals entering the market.

Custom Device Solutions

63 Device Design Will Act as Competitive Distinguisher in a Post-Patent Expiry Biosimilar Market

George I'ons dissects the different factors that will determine biosimilars' adoption and pace of advancement against their original counterparts, namely clinical confidence in the biosimilar and patient confidence in the drug delivery device.

Immunogenicity Testing

66 Regulatory Updates for Immunogenicity Assessment of Therapeutic Proteins

Leon Shi, PhD, Lan Li, MS, and Jing Shi, PhD, provide a high-level analysis of the significant changes to the guidance compared to the immunogenicity draft guidance released in 2016, and the implications for drug development programs.

Departments

Market News & Trends.....10
Technology & Services Showcase.....71

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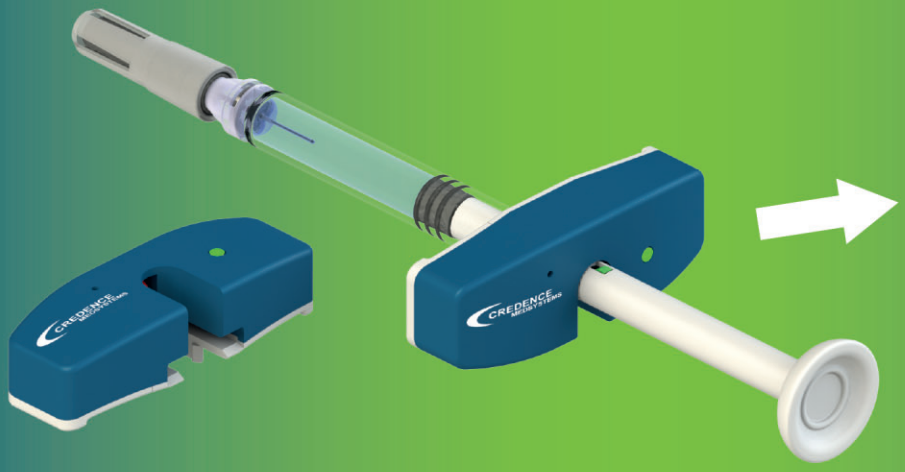

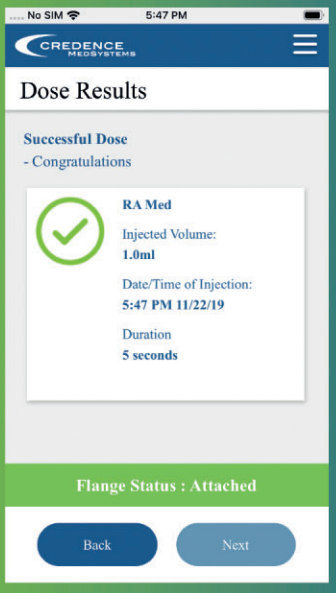

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Ajinomoto Bio-Pharma Services & DNDi Partner to Develop Critical Immunomodulator for Cutaneous Leishmaniasis Therapeutic

Ajinomoto Bio-Pharma Services recently announced a strategic supply partnership with the Drugs for Neglected Disease Initiative (DNDi), a collaborative, patients' needs-driven, non-profit drug research and development organization that is developing new treatments for neglected diseases, for the supply of a CpG oligonucleotide, as part of a combination therapy used in the treatment of cutaneous leishmaniasis infections. This project is supported by the Global Health Innovative Technology (GHIT) Fund.

As part of this partnership, Aji Bio-Pharma will manufacture CpG-D35, a class of CpG oligonucleotides, which provides a strong immunostimulatory effects. CpG-D35 will be used to stimulate innate immune response in patients as an adjunct to chemotherapies in treating complicated cutaneous leishmaniasis (CL) and post-kala-azar dermal leishmaniasis (PKDL), persisting parasitic infections causing severely disfiguring and stigmatizing skin lesions.

"We are excited to be able to collaborate on this oligonucleotide with DNDi and support them in their efforts to develop and supply this quality-of-life improving therapeutic for people with leishmaniasis," said Noriyasu Kataoka, Quality Manager and President, Ajinomoto Bio-Pharma Services Osaka. "We are pleased to be a trusted and innovative partner to our client, while reinforcing our dedication in improving the health of humankind."

Over 1 billion people are at risk of leishmaniasis worldwide, which is transmitted by sandfly bites. Cutaneous leishmaniasis is the most common presentation, with about 1 million new cases annually. Post-kala-azar dermal leishmaniasis is a complication of visceral leishmaniasis, which can appear months or years after completing treatment.

"We are very pleased to be partnering with Ajinomoto Bio-Pharma Services for the supply of promising new therapeutic for the treatment of cutaneous leishmaniasis," said Dr. Byron Arana, Head of Cutaneous Leishmaniasis Programme at DNDi. "With this partnership, we continue our goal to develop and provide safe and effective cutaneous leishmaniasis therapeutics."

Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization with sites in Belgium, US, Japan, and India, providing comprehensive development, cGMP manufacturing, and aseptic fill finish services for small and large molecule APIs and intermediates. Ajinomoto Bio-Pharma Services offers a broad range of innovative platforms and capabilities for pre-clinical and pilot programs to commercial quantities, including Corynex protein expression technology, oligonucleotide synthesis, antibody drug conjugations (ADCs), high potency APIs (HPAPI), biocatalysis, continuous flow manufacturing and more. Ajinomoto Bio-Pharma Services is dedicated to providing a high level of quality and service to meet our client's needs.

A not-for-profit research and development organization, DNDi works to develop new treatments for people living with neglected diseases, notably leishmaniasis, sleeping sickness (human African trypanosomiasis), Chagas disease, filarial infections, mycetoma, paediatric HIV, and hepatitis C.

The GHIT Fund is a Japan-based international public-private partnership fund (PPP) between the Government of Japan, multiple pharmaceutical companies, the Bill & Melinda Gates Foundation, the Wellcome, and the United Nations Development Programme (UNDP).

TriNetX Acquired by Carlyle Group to Help Advance Health Research Optimization

TriNetX recently announced global investment firm The Carlyle Group has made a strategic growth investment and will acquire a majority stake in the company. Terms of the transaction were not disclosed. Since its founding in 2013, TriNetX has built the largest global network of research hospitals and academic institutions, top biotech and pharmaceutical companies, contract research organizations (CROs), and other specialty data partners. TriNetX is powered by an impressive network of 170 healthcare organizations in 30 countries and used by more than 40 life sciences organizations, including 15 of the world's top 20 pharmaceutical companies.

"Our goal is to be on the desktop of every healthcare researcher in the world," said Gadi Lachman, CEO of TriNetX. "To accomplish this we need to continue to develop solutions to support clinical research at our healthcare organizations and bring more global data and technologies such as AI, machine learning and analytics to researchers so that they can ask more questions and generate more real-world evidence. Carlyle's investment accelerates our growth plans and will shorten the time it takes to turn our vision into reality."

TriNetX enables researchers to apply a data-driven approach to health research by providing web-based, on-demand access to harmonized global electronic health record (EHR) and claims data with a suite of highly intuitive analytics. TriNetX is utilized in all parts of the drug development cycle, including protocol design and feasibility, site selection and patient identification for clinical trials, as well as serving clinical research for drugs already in the market to help researchers understand efficacy, risks and other market dynamics and to generate real-world evidence (RWE) to support hypothesis and decision making, in real-time.

The longitudinal clinical and claims data representing over 400 million patients available through TriNetX is mapped to controlled terminology and consists of clinical facts from hundreds of healthcare organizations around the world, deep specialty data for all therapeutic areas, including COVID-19, cardiovascular, oncology, and rare disease, and linked medical claims, pharmacy claims and EHR data.

"With a deep clinical focus and a highly scalable data strategy, we believe TriNetX is well positioned for continued organic and inorganic growth opportunities," said Joe Bress, a Principal specializing in healthcare at The Carlyle Group. "We're excited to partner with Gadi and the TriNetX management team to help expand their global footprint and continue investing in the company's mission to advance the collective understanding of human health."

The investment in TriNetX is a continuation of Carlyle's long-term global commitment to healthcare, in which it has invested more than $15 billion of equity since inception. Equity capital for the investment came from Carlyle Partners VII, an $18.5 billion fund that makes majority and strategic minority investments primarily in the U.S. in targeted industries, including healthcare. SVB Leerink served as exclusive financial advisor to TriNetX.

Metrics Contract Services Begins $10-Million Plant Expansion

Metrics Contract Services recently announced it has commenced construction on the expansion of its novel oral solid dosage manufacturing facility expansion in Greenville, NC. The $10-million investment will add 3,760 square feet of production space to the current facility, providing added flexibility and capacity to the CDMO and its clients.

The expansion consists of three new rooms: one dispensing/flex room, one tablet press room and one flex room to accommodate the company's growing portfolio of commercial services following sustained increase in demand from clients for high potent handling capabilities.

New equipment also forms part of the investment and includes a Fette FE55 tablet press, a Bosch 720 encapsulator, which both offer containment capabilities for the safe handling of potent products, and a weigh and dispense isolator.

"The new equipment we've purchased is ideal for the small batch size and high changeover products which our clients require," said John Ross, President at Mayne Pharma US and Metrics Contract Services. "Our clients will see immediate benefits through higher yields and improved potent handling. We recognized that customer's commercial requirements often demanded increased flexibility within production suites. This expansion will cater for those needs because it creates more spaces where equipment trains can be tailored to the applicable process."

The expansion project which has been in development over the past 6 months is expected to be complete and fully operational by February 2021. Ross added "This is a significant investment for the business and reflects our commitment to increasing our novel oral solid manufacturing capabilities and providing our clients with quality services from initial concept through to global commercialization. We are now actively looking at the next phase of investment and how to maximise the expanded facility even further with the potential addition of further packaging and adjacent formulation technologies."

Metrics Contract Services offers quality pharmaceutical formulation development; clinical trial materials manufacturing for all phases; analytical method development and validation services and commercial scale manufacturing and specializes in highly potent, novel oral solid dosage forms.

Metrics Contract Services is a full-service pharmaceutical development and manufacturing organization serving clients worldwide delivering proven scientific and operational excellence for novel oral dosage forms.

Metrics' areas of expertise include quality pharmaceutical formulation development; first-time-in-human formulations; Phase 1-3 clinical trial materials manufacturing; and analytical method development and validation services leading to commercial scale manufacturing.

Technical capabilities include highly potent, cytotoxic and unstable compounds; Schedule II-V controlled substances; and products with poor bioavailability, for which we offer an impressive portfolio of advanced delivery methods. Located in Greenville, N.C., Metrics is a proud member of Mayne Pharma. For more information, visit metricscontractservices.com.

Arctoris & Syntekabio Form Drug Discovery Research Partnership

Arctoris has recently signed a Memorandum of Understanding with listed Korean company Syntekabio, Inc. to collaborate on drug discovery efforts. The first project under the agreement sees the two companies work together to assess small molecule therapeutics for COVID-19.

The MoU brings together two highly complementary technologies: Syntekabio is a leading AI-driven drug discovery company that uses machine learning and supercomputing to discover new drugs, and Arctoris is a British technology company that has developed a fully automated drug discovery platform enabling rapid generation of high-quality drug discovery data. Syntekabio will use Arctoris' unique technology platform for biochemical and cell-based experiments including target-based assays and viability assessments.

Access to the Arctoris platform enables the company's clients and partners to conduct their drug discovery processes in full automation. Available services include data-set generation for AI model training and validation, hit-to-lead, lead optimization and candidate selection.

Under the terms of the MoU, Syntekabio and Arctoris work together to identify and screen a series of potential candidate molecules for COVID-19 treatment, not only saving development time, but also ensuring a greater degree of confidence in the experimental results.

Martin-Immanuel Bittner, MD, DPhil, CEO of Arctoris, said "This partnership highlights the utility and capability of the Arctoris approach to drug discovery. Thanks to our robotic technology platform, we can significantly accelerate the identification of candidates for COVID-19 treatment. By combining the novel technologies developed by Arctoris and Syntekabio, we aim to develop potential new treatments faster – for COVID-19 and beyond."

Sunil Youn, MD, Director of Business Development of Syntekabio, added "Syntekabio is a leader in AI-driven drug discovery. We are pleased to collaborate with Arctoris, enabling us to rapidly validate our in silico predictions. Together, we can reach the next drug discovery milestones faster."

The MoU with Syntekabio is the latest in a series of partnerships formed by Arctoris this year, which includes publicly announced partnerships with Insilico Medicine and Molecule.

Arctoris Ltd is an Oxford-based research company that is revolutionizing drug discovery for virtual and traditional biotechnology companies, pharmaceutical corporations, and academia. Arctoris has established the world's first fully automated drug discovery platform, offering pre-optimized and fully validated processes for its partners and customers globally.

Syntekabio, Inc. is an AI and NGS-based drug development company, utilizing a genomic database and artificial intelligence to predict and identify new molecular entities to be a relevant new drug product. It is the global first AI drug development company listed on the public market (KOSDAQ: 226330) in December 2019. The company's lead product candidate, STB-C017, an IDO/TDO dual inhibitor for the treatment of advanced solid tumors, is in preclinical development. The company's subsequent pipelines include personalized neoantigen cancer vaccines, small molecules targeting established oncology targets, and biomarkers to stratify relevant patients to maximize treatment efficacy.

Orasis Raises $30 Million to Advance Clinical Development Program

Orasis Pharmaceuticals recently announced the closing of a $30-million Series C financing. The financing was co-led by new investor Bluestem Capital and returning investor Visionary Ventures, with participation from other returning investors Sequoia Capital, SBI (Japan) Innovation Fund, Maverick Ventures, LifeSci Venture Partners, and additional investors. Tyler J. Stowater, Partner and Vice President of Bluestem Capital, will join the Orasis Board of Directors in conjunction with the financing.

Proceeds from the financing will be used to advance Orasis' lead eye drop candidate for the treatment of presbyopia symptoms through completion of its Phase 3 clinical trials. The funds will also be used for pre-commercialization activities ahead of potential product launch.

"This successful funding round completes the capitalization for the Phase 3 clinical trials and fuels the initial growth strategy for commercialization," said Elad Kedar, Chief Executive Officer of Orasis. "We aspire to make near vision clear again for people with presbyopia by empowering them with an unparalleled solution, an eye drop that will provide them with comfort and control of their near vision. We are very grateful for and highly encouraged by the validation from a diverse range of investors, including the co-lead investors Bluestem Capital and Visionary Ventures, and our returning investors. Our product candidate has demonstrated excellent efficacy, safety, and comfort profiles in previous clinical studies, and we look forward to initiating our Phase 3 clinical trials to further evaluate the effectiveness of the product in the near future."

Tyler J. Stowater, Partner and Vice President of Bluestem, added "With almost 2 billion people in the world living with presbyopia, the market potential for a novel, non-invasive option is highly anticipated by eye care providers and patients. We have high confidence in the Orasis team, to successfully complete its clinical program, and apply their informed commercial approach, which will make Orasis a leader in the presbyopia space."

Presbyopia is the loss of ability to focus on near objects as a result of the natural aging process. It occurs mostly after the age of 40 when the crystalline lens of the eye gradually stiffens and loses flexibility. There are almost 2 billion people globally and more than 120 million people in the US living with presbyopia. People with presbyopia experience blurred vision when performing daily tasks that require near visual acuity, such as reading a book, a restaurant menu, or messages on a smartphone. Presbyopia cannot be prevented or reversed, and it continues to progress gradually. All existing treatment options are either cumbersome or invasive, presenting a significant unmet need for quality of life improvement for people with presbyopia.

Orasis is an emerging ophthalmic pharmaceutical company committed to making near vision clear again for people with presbyopia. Orasis' novel proprietary formulation, designed to achieve an optimal balance between efficacy, safety, and comfort, has the potential to position the company as an emerging leader in the presbyopia space.

Aqualung Therapeutics Awarded NIH Fast-Track Award

Aqualung Therapeutics, an early stage biotech company developing an immune-focused, anti-inflammatory therapeutic platform for unchecked inflammation in patients with serious acute and chronic diseases, has been awarded a 1-year NIH FAST-TRACK AWARD (1R41 HD101202-01A1) to support development of a humanized antibody therapy for pregnant women with intrauterine infection at risk for preterm birth.

Each year, more than 400,000 preterm births occur annually in the US, the majority born to mothers with "chorioamnionitis" or intrauterine infection that occurs before or during labor. The name refers to the infection of the membranes surrounding the fetus: the "chorion" (outer membrane) and the "amnion" (fluid-filled sac) leading to a preterm birth and/or serious infection in the mother and the baby. Preterm births are at risk for a myriad of serious lung, gastroenterology, and cognitive complications as well as developmental delays.

Aqualung Therapeutics (ALT) scientists have identified extracellular NAMPT or eNAMPT, a master regulator of tissue and systemic inflammation as a novel therapeutic target in Chorioamnionitis. ALT has demonstrated robust NAMPT expression in placentas from women with chorioamnionitis. In a preclinical pregnant mouse model of ChorP, a eNAMPT-neutralizing antibody was dramatically protective, improving preterm birth mortality and inflammation in newborn pups.

This NIH STTR Award will drive the final selection of the lead eNAMPT-neutralizing humanized therapeutic mAb between two candidates, ALT-100 and ALT-200; with selection utilizing in vitro and preclinical in vivo models of chorioamnionitis. Upon confirmation of the optimal mAb candidate in treating chorioamnionitis, Aqualung will submit an R42 STTR grant to further support pre-clinical development and IND-enabling studies.

"This is the fourth NIH-supported indication for development of the eNAMPT platform along with ARDS, pulmonary hypertension and radiation lung injury. We are excited the NIH sees the value of our science and is willing to fund our early proof of concept development," states Stan Miele President of Aqualung Therapeutics.

Aqualung is an early stage biotech company developing immune-focused therapeutic antibodies for patients suffering from disorders characterized by acute and chronic lung and systemic inflammation. Founded in 2016 and led by a physician scientist, Aqualung's science-driven approaches led them to the identification of nicotinamide phosphoribosyltransferase (NAMPT) and other key proteins expressed in both acute and chronic inflammatory diseases. Aqualung Therapeutics is developing eNamptor, a Next Gen platform comprised of : i) ALT 100/200, humanized eNAMPT-neutralizing monoclonal antibodies; ii) eNAMPT-Plex, a plasma-based biomarker panel comprised of cytokines, including eNAMPT, which predicts ARDS mortality; and iii) NAMPT-Gene, a genotyping assay that identifies individuals at increased risk for ARDS death. The pipeline of ALT is designed to target a range of diseases, including ARDS, ventilator- and radiation-induced lung injury, chorioamnionitis, prostate cancer, pulmonary hypertension, and both pulmonary and hepatic fibrosis (NASH). These conditions all exhibit a significant unmet medical need with significant morbidity and mortality.

OXGENE Introduces TESSA Technology for Robust & Reproducible AAV Manufacture at Scale

OXGENE recently announced the launch of its scalable, plasmid-free manufacturing system for AAV. OXGENE's new TESSA technology addresses industry-wide challenges associated with robust and reproducible AAV manufacture at scale. These include high cost of goods, and low packaging efficiency. TESSA aims to deliver a paradigm shift in scalable AAV manufacture.

Adeno-associated virus, or AAV, is a popular choice of viral vector to deliver gene therapies to patients, owing to its low immunogenicity, favorable safety profile, and the ease with which it transduces numerous cell and tissue types. However, manufacturing systems have not kept pace with biological advances, leaving these therapies costly, difficult to produce at scale, and subject to inherent batch-to-batch variability. This represents a serious challenge to regulators and health authorities when it comes to approving these treatments for clinical use.

OXGENE's TESSA technology overcomes manufacturing obstacles by taking advantage of AAV's natural relationship with another virus — the adenovirus. In nature, AAV co-exists with adenovirus, which provides the "help" AAV needs to replicate. However, as well as replicating the AAV, the adenovirus also replicates itself, leading to high levels of adenoviral contamination if this process is translated to an industrial context.

OXGENE has addressed these challenges by manipulating the adenoviral life cycle so that it can still provide high quality help for AAV replication, but is unable to manufacture itself, reducing adenoviral contamination by 99.9999% in a manufacturing run. Integration of the AAV rep and cap genes into the adenoviral vector means that everything required for AAV production, except the AAV genome, can be provided in a single viral vector. Meanwhile, the AAV genome can either be encoded within a second TESSA vector, in a plasmid, or within an AAV particle itself. Using two TESSA vectors improves yields of AAV2 by 40-fold, accompanied by a 2000-fold increase in particle infectivity compared to a standard three-plasmid manufacturing approach.

Once this first AAV seed stock has been produced, co-infecting cells with this AAV alongside another TESSA vector can further amplify the AAV in a simple, reproducible and scalable manner, removing the reliance on expensive and limiting plasmids for AAV manufacture.

OXGENE's CEO, Dr Ryan Cawood, said "The gene therapy industry's reliance on plasmids is a major limitation for robust and reproducible large-scale AAV manufacture. By taking a 'back to nature' approach to rethink AAV production from the ground up, we've developed a truly innovative new technology that we expect to transform the way AAV is manufactured. By combining high AAV yields with scalability, packaging efficiency and increased infectivity, we hope that TESSA technology will help to bring down the overall cost of goods involved in gene therapy development. We hope it will also improve the safety of the final therapeutics, as the higher quality, more infectious AAV resulting from TESSA based manufacture could mean significantly lower effective doses."

T-knife & Catalent Sign Technology Transfer & Manufacturing Agreement

T-knife GmbH and Catalent recently announced they have signed an agreement to provide technology transfer and CGMP clinical manufacturing of T-knife's T1367 T-cell receptor (TCR) program.

T1367 is an autologous T-cell receptor-based cell therapy derived from T-knife's proprietary humanized T-cell receptor (HuTCR) mouse platform and specifically targets MAGE-A1 positive tumors in cancer patients. The therapy is expected to be manufactured for clinical trials in both the European Union and the US.

Under the terms of the agreement, Catalent will undertake transfer of T-knife's platform process for T-cell receptor-based cell therapy at its site in Gosselies, Belgium, with the goal of manufacturing clinical batches for European trials in 2021. T-knife will also prepare for the transfer of the TCR manufacturing platform to Catalent's Houston, Texas, facility with a view to initiating clinical trials in North America in the future.

"The product candidates based on our proprietary HuTCR platform require sophisticated, state-of-the-art manufacturing capabilities and deep cell and gene therapy know-how," said Michael Buchholz, Director Manufacturing of T-knife. "We are convinced that Catalent is the right partner for T-knife to ensure premier manufacturing of our pipeline programs, covering all stages from clinical trials to market."

"Catalent is well-suited to support T-knife with focused technology transfer and process industrialization in both Gosselies and Houston," added Manja Boerman, PhD, President, Cell & Gene Therapy, Catalent. "Emerging and innovative treatments like T1367 are moving rapidly to the clinic. Catalent is committed to continual investment and expansion to support our clients as they continue on the journey to commercialization."

Catalent's 2,400-square-metre (25,830-square-foot) facility in Gosselies, Belgium, provides clinical through commercial-scale cell therapy manufacturing, for both autologous and allogeneic cell therapy treatments. The facility accommodates four process development laboratories, nine flexible manufacturing clean rooms for cGMP manufacturing, as well as fill and finish services and quality control laboratories. An additional large-scale commercial manufacturing plant is currently under construction at the site and expected to be fully commissioned in 2021. The company also has a clinical manufacturing site in Houston, which is under qualification and expected to be fully commissioned in 2020.

T-knife is a next-generation adoptive T-cell company utilizing its proprietary humanized T-cell receptor (HuTCR) mouse platform technology to treat solid tumors. It was founded as a spin-off from Max-Delbruck Center for Molecular Medicine together with Charité University Hospital in Berlin in 2018. T-knife´s mission is to use its unique technology to bring highly effective and safe T-cell receptor-based therapeutics to market. Based on the unparalleled T-cell immunology expertise of its founders and the unique and proprietary HuTCR platform, the Company develops fully human TCRs which are expected to set new technology standards and to provide superior safety and efficacy.

Hovione Announces Partnership to Produce Ligand's Captisol; Used in Gilead's Covid-19 Treatment

Hovione recently announced the signing of a partnership agreement with Ligand to significantly ramp up the production output of Captisol, a Ligand product, which is a chemically modified cyclodextrin proven to improve the solubility and stability of drugs. It is used in the formulation of Gilead's Covid-19 treatment Veklury (remdesivir). Hovione is the sole producer of this key enabling excipient.

"To meet Captisol demand associated with Veklury, Hovione will soon be producing per month the quantity it usually produces in 1 year. This sudden spike in demand has required unique mobilization efforts across the Hovione network to secure additional raw material supply, execute major capital expenditure projects at our sites, maximize operational efficiency, hire additional talent, and identify external partners to expand our overall capacity. The pharmaceutical supply chain is working together in an unprecedented fashion to treat patients and save lives. Hovione is privileged to be part of this truly global response," said Jean-Luc Herbeaux, Chief Operating Officer.

"Ligand values its long-standing partnership with Hovione," added Matt Foehr, President and Chief Operating Officer of Ligand. "Their excellent customer service, global commitment to quality, and high pharmaceutical standards make them an ideal partner for Captisol, a critical component for a number of life-saving medicines. We commend them for responsibly and efficiently partnering with Ligand to manage the scale up and expansion of their operations to contribute to global health during the pandemic."

Ligand's Captisol technology is a patent-protected, uniquely modified cyclodextrin, with a chemical structure that was rationally designed to enable the creation of new products by significantly improving solubility, stability, bioavailability, and dosing of active pharmaceutical ingredients (APIs). It uses a green manufacturing process that uses water as process solvent.

Gilead Sciences' Veklury is an investigational nucleotide analog with broad-spectrum antiviral activity both in vitro and in vivo in animal models against multiple emerging viral pathogens. Multiple ongoing international Phase 3 clinical trials are evaluating the safety and efficacy of Veklury for the treatment of SARS-CoV-2 infection, the virus that causes COVID-19, in different patient populations, formulations, and in combination with other therapies. The US FDA expanded the Emergency Use Authorization (EUA) enabling use of the investigational antiviral Veklury to treat all hospitalized patients with COVID-19, in addition to the previous authorization for patients hospitalized with severe COVID-19.

Hovione is an international company with over 60 years of experience as a Contract Development and Manufacturing Organization (CDMO) and is currently a fully integrated supplier offering services for drug substance, drug product intermediate, and drug product. With four FDA inspected sites in the US, China, Ireland, and Portugal and development laboratories in Lisbon, Portugal, and New Jersey, US, the company provides branded pharmaceutical customers services for the development and compliant manufacture of innovative drugs, including highly potent compounds.

CombiGene & Cobra Biologics Sign Agreement to Secure GMP Production of Plasmids for Production of Gene Therapy

Cobra Biologics and CombiGene AB (publ) (CombiGene) recently announced they have signed agreements covering Good Manufacturing Practice (GMP) production of two essential plasmids needed for the manufacture of CG01, a gene therapy designed for the treatment of drug resistant focal epilepsy.

The GMP production of two essential plasmids, derived from master cell banks, represents a crucial development in the production of CG01 for the first clinical study. Increasing production of plasmids to large scale and according to GMP requires management of the scale-up process to ensure plasmids are of therapeutic-grade quality. Cobra's long-established plasmid production platform along with in-house expertise will ensure high quality plasmids are produced for CG01.

The agreement follows the recent announcement that Cobra had successfully completed production of the GMP master cell banks to produce three plasmids used as starting material for CombinGene's gene therapy vector, CG01.

Jan Nilsson, CEO of CombiGene, said "The fact that CombiGene has now signed an agreement with Cobra regarding the production of two plasmids is very positive as we thus secure access to crucial components for the production of CG01. Cobra has consistently delivered in terms of both time and quality and it is therefore very satisfactory that they will now be responsible for the production of this important part in the production of CG01. Through this agreement with Cobra, we are taking another step closer to clinical studies."

Peter Coleman, Chief Executive of Cobra Biologics, added "We are excited to continue the journey with CombiGene and this agreement is the next big step in the production of CG01. We have a well-established plasmid production platform and in-house expertise in quality control that will ensure the delivery of GMP quality plasmid."

CG01 is a gene therapy developed to treat drug-resistant focal epilepsy. Every year, approximately 47,000 drug-resistant patients with this type of epilepsy are estimated to be added in the United States, EU5, Japan and China. CombiGene believes that it is realistic that 10-20 percent of these patients could be treated with the company's gene therapy. The global market for drug candidate CG01 is estimated at $750 million to 1 .5 billion annually.

Cobra Biologics, together with its parent company Cognate BioServices, is a leading international contract development and manufacturing organisation (CDMO) providing the highest quality development and manufacturing services for the cell and gene therapy fields, ranging from early stage development and preclinical services to clinical and commercial supply. Cobra and Cognate service an international customer base from its manufacturing and development facilities in the UK, Sweden, and the US.

CombiGene's vision is to offer patients affected by severe life-changing diseases opportunities for a better life through innovative gene therapies. CombiGene's business concept is to develop effective gene therapies for serious diseases that today lack adequate treatment methods.

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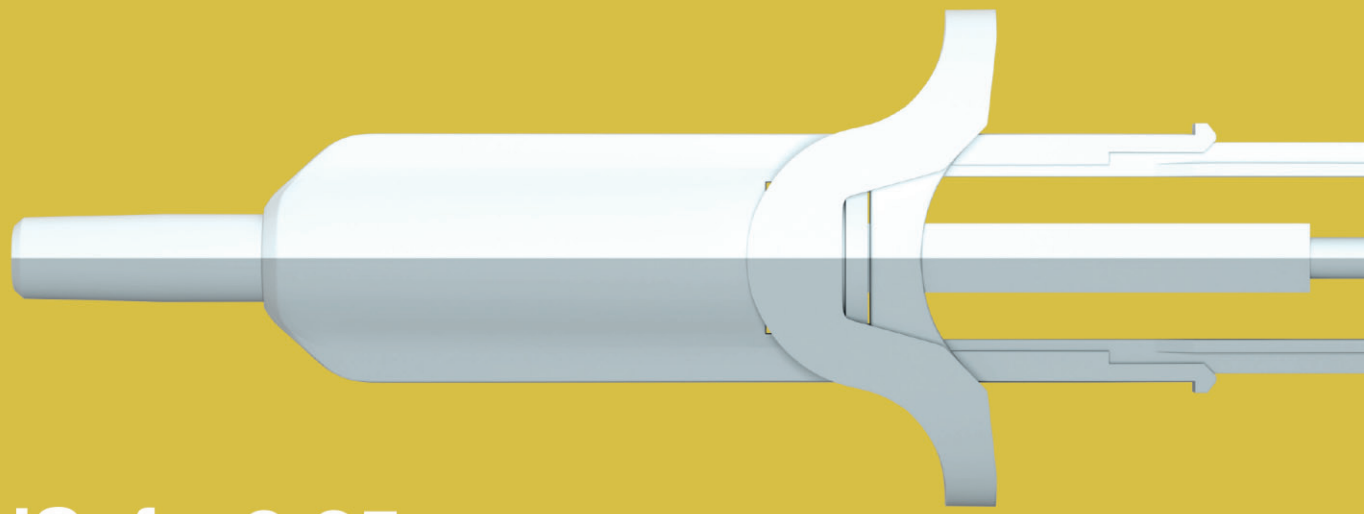

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ASSAY DEVELOPMENT

Case Study: How Custom Assay Development Helped Spur Precision Medicine Research in Multiple Myeloma

By: Steven Gross, MS

INTRODUCTION

From big pharma to emerging biotech companies, a robust assay is an integral part of any pharmaceutical company's drug discovery and development process. Yet many organizations may not want to devote the substantial time or resources required to develop custom, reproducible assays on their own. For these companies, having a trusted laboratory partner with the necessary expertise and technology can make all the difference – both in creating assays for specific biomarkers and in successfully integrating these assays into clinical trials in a more cost-effective manner.

Starting in 2010, the Menarini Silicon Biosystems, Inc. (MSB) R&D team (then part of Veridex, a Johnson & Johnson company) led the process of developing their first assay to isolate and enumerate circulating multiple myeloma cells (CMMC) from peripheral blood. Our primary goal for the assay was to determine if CMMCs could be used to better understand the biology of multiple myeloma and monitor clinical progression of the disease. The assay was developed in collaboration with Janssen Oncology Pharmaceuticals as part of a research agreement.

The following provides a "behind-the-scenes" look at the CMMC assay development process (from 2010 through today) to show how pharmaceutical companies can effectively partner with a laboratory to design customized assays that complement their drug discovery and development programs.

TECHNOLOGY & EXPERTISE: THE POWER OF CELLSEARCH

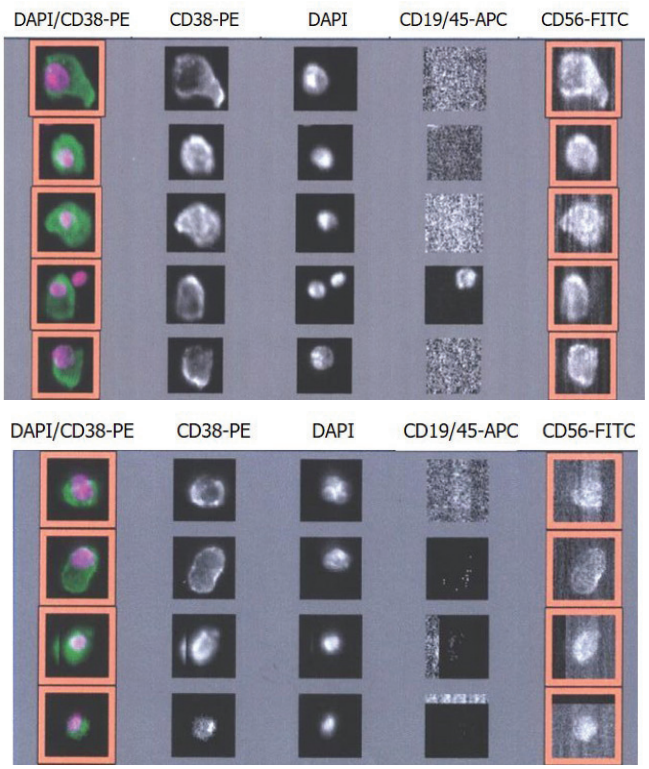
When selecting a partner for assay development, both the technology and expertise of those in the lab are important factors to consider. Our team developed the circulating multiple myeloma cells (CMMC) assay with the CELLSEARCH® platform, which is considered the gold standard of liquid biopsy technology for detecting circulating tumor cells (CTCs). It is the first and only clinically validated, FDA-cleared system for identification, isolation, and enumeration of CTCs in metastatic breast, metastatic prostate, and metastatic colon cancer.

The CELLSEARCH system uses automated sample capture and analysis on a four-color semi-automated fluorescence microscope. It separates rare CTCs from blood using ferrofluid nanoparticles coated with antibodies to target the epithelial cell adhesion molecule (EpCAM), a protein expressed on the surface of epithelial cells. EpCAM is expressed at a high level by solid tumors and has allowed researchers to develop assays for cancers like prostate and breast cancer. The cells are then stained with detection antibodies and an antibody to exclude leukocytes, and image analysis is carried out to identify tumor cell candidates. The technology is not limited to EpCAM-expressing cells, however. We can develop custom ferrofluids to capture non-EpCAM-expressing cells, and MSB has additional kits targeting circulating endothelial cells (CEC kit) and circulating melanoma cells (CMC kit).

With a fourth detection channel available for additional screening of cells, the system has built-in flexibility to move beyond just counting cells and incorporate other markers such as PD-L1, HER2, and EGFR. As we did with Janssen, pharmaceutical companies could use a primary detection marker for CTCs, while using the open channel to look for the expression of a specific target marker as inclusion criteria for a clinical trial, or to monitor the therapeutic effect of a drug.

By working with our R&D team, the Janssen group also had the benefit of working with some of the same people who created the CELLSEARCH platform and pioneered the development of custom assays with the technology. Many of us were part of a group of researchers, led by Massimo Cristofanilli, MD, that helped validate the CELLSEARCH technology in the early 2000s. That research established that the number of CTCs before treatment was an independent predictor of progression-free survival and overall survival in patients with metastatic breast cancer.[1] When it comes to rare cell or CTC assay biomarker development, this is a level of expertise not available at an average reference laboratory.

FIGURES 1A&B



Images of myeloma cell line H929 (A) and cells from a Multiple Myeloma patient (B) captured with the CMMC kit and stained with CD56FITC in the open channel.

THE CMMC ASSAY DEVELOPMENT PROCESS

Multiple myeloma is the second most common hematological cancer in the US, with an estimated incidence of over 20,000 new cases per year. Despite advances in treatment, the disease remains incurable with a 5-year survival rate of only 45%.

In 2010, Janssen's hematology group asked our team to develop an assay for the detection and enumeration of CMMCs from peripheral blood samples. The desire for the assay was spurred by a growing body of research that showed the presence of CMMCs in patients with the disease, as well as those with two precursor diseases: monoclonal gammopathy of unknown significance (MGUS) and smoldering multiple myeloma (SMM). It was recognized that those circulating cells might be usable as a liquid biopsy to learn more about the progression of the disease and identify actionable mutations for targeted therapy without an invasive bone marrow biopsy. In addition, the ability to access CMMCs through a simple blood draw means we can capture these cells more easily than with bone marrow biopsies, which could potentially make it possible to monitor the disease in real time.

Because much of assay development can be a trial-and-error process, we used a phased approach to minimize risk for Janssen. For each of the three phases (feasibility, verification, and final development), we submitted reports and obtained approval from Janssen before moving on to the next phase.

THE CHALLENGE: IDENTIFYING DETECTION & CAPTURE ANTIBODIES

The initial phase of the CMMC assay development process began in February 2010. Developing the first assay for a hematological cancer presented a distinct challenge for our team. Capture and detection of tumors that typically express EpCAM is relatively straightforward on the CELLSEARCH platform. Most blood cancers, on the other hand, do not have unique markers that differentiate them from normal white blood cells in circulation.

In order to develop the assay, our CTC experts collaborated with Janssen's multiple myeloma experts to identify antibodies that would allow for the detection and capture of the CMMCs. Fortunately, multiple myeloma is one of the few hematologic cancers that have a marker unique enough to identify the cell: CD138. We chose to use CD138 as the capture antibody and CD38 for detection, with CD19 and CD45 as exclusion antibodies.

FIGURES 2A&B

Now available as a laboratory service at Menarini Silicon Biosystems, the CMMC assay is part of a broad menu of assays, including tests for enumeration of epithelial cells, endothelial cells, melanoma cells, and breast cancer cells expressing PDL-1. The assays use the CellSave tube, which stabilizes the sample for up to 96 hours at ambient temperature and allows shipment of samples from remote locations for analysis and improves the reproducibility and reliability of CTC analysis.

THE STRUGGLE: UTILIZING THE OPEN CHANNEL

Next, a great deal of discussion went into selecting a marker for identification in the open channel. While the available literature offered a wide variety of markers used in multiple myeloma, we wanted to select the most common ones in order to pick up the highest percentage of patients with the disease.

Ten years ago, most diagnostic testing for multiple myeloma was done in bone marrow, but finding those same cells in circulation can be a difficult process. Some markers may not be ideal for testing cells in peripheral blood. Though our team finally decided on a marker for the open channel, it turned out that marker was not found frequently on CMMCs in the circulation. While the cells were positive for that marker in the bone marrow, when they moved into circulation, we discovered they tended to lose that marker. That part of the assay was subsequently dropped from development.

THE RESULT: A REPRODUCIBLE CMMC ASSAY

By March 2011, our team succeeded in developing an automated assay capable of reproducibly isolating CMMCs from the peripheral blood of patients with multiple myeloma. The assay provided valuable information regarding how the number of CMMCs changed with progression of the disease, or in response to treatment.

In the final phase of development, our group transferred the assay to the clinical development team. Both groups carried out side-by-side testing to make sure the results matched, and then trained team members on the assay so they could run it independently.

In 2018, we published results of a study based on the CMMC assay in The British Journal of Hematology.[2] Our research indicated the assay could be used to investigate the biology of the disease and potentially monitor progression, especially in early stage asymptomatic disease.

In the study, we counted CMMCs from over 1,000 patient samples, including those with newly diagnosed MM and SMM. In the newly diagnosed patients, CMMC counts correlated with other clinical measures of disease burden, including percentage of bone marrow plasma cells, serum M protein, and International Staging System stage. Patients with CMMC counts equal to or greater than 100 in 4 ml of blood during remission had worse progression free survival compared with patients who had less than 100. Those with undetectable CMMCs had even greater overall survival benefits. Patients with SMM showed a trend toward higher-risk myeloma states with higher CMMC counts.

ASSAY & EXPERTISE TRANSFER TO MENARINI LAB SERVICES

In 2017, Menarini Silicon Biosystems acquired CELLSEARCH from Janssen. This marked the transfer of the CMMC assay to Menarini's Laboratory Services, which provides global laboratory testing with the CELLSEARCH platform, from Phase I to Phase III clinical trials. With a CLIA-certified and ISO15189-accredited lab in the US and a mirror lab in Italy, as well as its proprietary CellSave tube, which stabilizes samples for 96 hours to enable international shipping, MSB partners with clinical investigators and pharmaceutical companies throughout the world to perform global clinical trials.

A majority of the R&D team that originally developed the CMMC assay also became part of Menarini. With nearly two decades of pharma services development and clinical trial testing experience, our Assay Development and Lab Services teams have created close to a dozen custom assays and participated in testing for nearly 100 clinical trials.

We continue to use our expertise with the CELLSEARCH platform to develop custom assays, helping our partners make the best use of the technology in order to develop companion diagnostics that can accelerate the validation of personalized therapies. By using the only FDA-cleared CTC platform, our partners who use their data for FDA submissions are confident in the quality and reproducibility of their assays.

CUSTOM ASSAY DEVELOPMENT

The CMMC assay is now available as a laboratory service, part of a broad menu of assays available to Menarini's pharmaceutical and academic partners. Other CLIA-regulated tests on the menu include tests for enumeration of epithelial cells, melanoma cells, and breast cancer cells expressing PDL-1.

These assays are designed in collaboration with company scientists and can be customized for many different types of cells, based on the target of the trial. The system can be tailored to detect different types of tumor cells in the same way that it was tailored to capture and detect CMMCs.

After developing the assay for a particular biomarker of interest, we can also provide information beyond just the number of cells captured, depending on the specific parameters of the clinical trial. Although the available open channel on the CELLSEARCH platform ultimately wasn't needed for the CMMC assay, it offers potential for even more selectivity for assay development. Using that channel, we can look for the expression of the marker to verify patient eligibility for the trial, or monitor how that expression changes before, during, and after therapy to determine the therapeutic effect of the drug being studied.

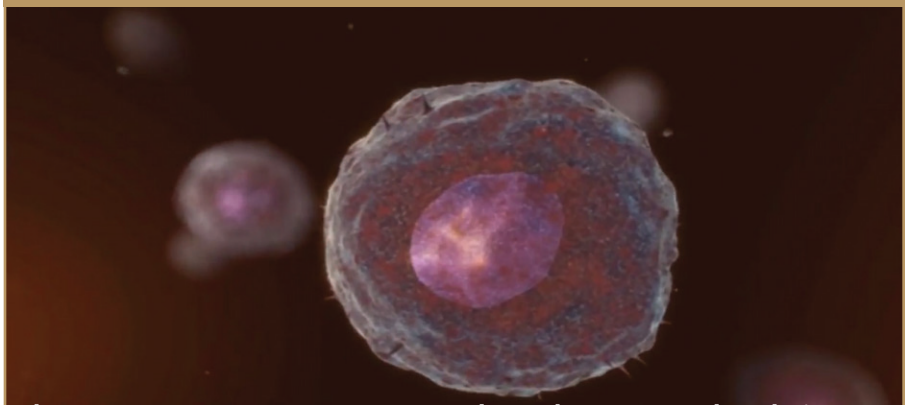
Similar to the development process for the CMMC assay, we approach custom assay development in phases. If at any point we conclude the assay won't work, the company does not have to pay to proceed to the next phase of development. This gives our R&D team the opportunity to explore new, novel markers and develop innovative assays while minimizing the financial risk for our partners.

A MORE COMPLETE LIQUID BIOPSY

With the addition of Menarini's DEPArray™ technology to the assay workflow[3], the possibilities for customized enumeration, isolation, and molecular characterization of rare cells are even greater. DEPArray is an automated image-based cell selection platform that can recover single cells of interest from heterogeneous samples for downstream molecular analysis. Combining this functionality with CELLSEARCH allows further identification, isolation, and characterization of cells of interest based on a wide range of parameters, including cell characteristics, expression analysis, mutations, next-generation sequencing, and more.

With the CMMC assay, the CELLSEARCH platform can separate the cells from a blood sample, producing an enriched population of CMMCs to be analyzed with the DEPArray technology, which enables molecular characterization of those individual cells in real-time. Not only does the workflow[3] allow the researchers to monitor the number of CMMCs, it also enables them to observe the specific molecular changes that occur throughout the disease progression, which will likely have therapeutic implications for this rapidly moving, dynamic cancer.

FIGURE 3



The CELLSEARCH system uses automated sample capture and analysis on a four-color semi-automated fluorescence microscope. It separates rare CTCs from blood using ferrofluid nanoparticles coated with antibodies to target EpCAM cells.

PUSHING PRECISION MEDICINE FORWARD

In 2020, Menarini Silicon Biosystems will launch the CMMC assay as a research-use-only commercial kit. Like the development of the original assay, this process was not without its challenges, including the need to design a more stable capture reagent when it was discovered that CD138 alone was not stable enough for commercial use. To address this at the time, our team developed a modified capture reagent that combined both CD138 and CD38. The CMMC RUO kit will be used with a new research-use-only blood collection tube containing a new blood preservative that helps stabilize CD138. This eliminates the need for the CD138/38 hybrid capture reagent, which results in significantly lower background.

By offering the CMMC assay as a kit that researchers can run on their own instrumentation, the hope is that it will open new doors on further investigating these cells. As researchers learn more about the molecular dynamics of multiple myeloma, this could have a significant impact by helping to identify patients that will respond to an already existing drug, or lead to the development of new, more effective treatments, an important step forward for precision medicine research.

ACKNOWLEDGEMENT

The author would like to thank the members of the Menarini Silicon Biosystems R&D group, clinical group, and the commercial team for their contributions to the development of the CMMC assay. ◆

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3. The workflow described is for research use only. Not for use in diagnostic procedures. The performance characteristics, safety, and effectiveness of the workflow have not been established and are not cleared or approved by the FDA. The CMMC Assay and the associated blood collection tube used for the detection of CMMCs is for research use only. Not for use in diagnostic procedures.The DEPArray technology is for research use only. Not for use in diagnostic procedures.

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BIOGRAPHY

Steven Gross is the Head of Assay Development for Menarini Silicon Biosystems. As a Scientist/Senior Scientist, he has been a part of the CELLSEARCH story from its founding at Immunicon Corporation, then with Johnson & Johnson, and now Menarini Silicon Biosystems. In addition to executing R&D research agreements and assay development, he works closely with both the clinical and commercial teams to supply reagents for clinical lab services and interact with research partners and customers. He earned his Master's degree in Biology from Temple University in Philadelphia.

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PEGYLATION

PEGylation - Three Decades of Product Approvals & Technology Development

By: Esay Okutgen, PhD, Alper Orhan MSc, and Josef Bossart, PhD

INTRODUCTION

With the 30-year anniversary of the first product approval using PEG (polyethylene oxide polymer) conjugation, Enzon's Adagen (pegadamase), it seems an appropriate occasion to review the evolution of the technology (PEGylation) and subsequent product approvals. PEGylation refers to the conjugation of PEG to biologically active molecules with the objective of enhancing the therapeutic performance of these molecules. The more important benefits of PEGylation are to extend drug half-life and reduce host immune responses. This latter benefit was critical for the development of the first two approved PEGylated products, Enzon's Adagen, a bovine-derived adenosine deaminase for the treatment of severe combined immune-compromised deficiency (SCID), and Oncaspar, E. coli-derived asparaginase, for the treatment of pediatric acute lymphoblastic leukemia (ALL).

IN THE BEGINNING

Adagen and Oncaspar, both non-human enzymes, depend on PEGylation to reduce the immune response that limits their therapeutic usefulness. They use a PEGylation strategy that involves the non-specific attachment of multiple, relatively small, 5-kDa PEG molecules. This non-specific attachment strategy, under the proper experimental conditions, does not significantly disrupt the active site of the enzyme but does suppress the undesired immune response.

In contrast, the next PEGylated products to be approved, PegIntron and Pegasys, depend primarily on PEGylation to extend the circulating half-life of the parent proteins, interferons for the treatment of Hepatitis C. In addition to extending the dosing frequency from three times weekly to once weekly, both PEGylated products have demonstrated improved efficacy and tolerability in comparison with the unPEGylated proteins. These products are notable because they were the first approved products using a strategy of a limited number of larger PEG molecules attached in a relatively specific manner. This approach retains the activity of the cytokines while extending their circulating half-life. PegIntron and Pegasys use somewhat different strategies in terms of PEG polymer size and geometry. Schering-Plough's PegIntron, using Enzon- developed technology, attaches a single 12-kDa linear succinimidyl carbonate PEG (SC-PEG) to amino groups, with as many as 14 different positional isomers. Roche's Pegasys, developed with Shearwater technology, features a single 40- kDa branched SC-PEG linked to amino groups with four positional isomers. Approval of the two competing products resulted in patent challenges that were resolved with a cross license of intellectual property between Shearwater, Inhale Therapeutics at the time, and Enzon.[1] Excellent discussions of these and other PEGylation strategies are provided in several review articles.[2-4]

These two approaches, multiple non-specific small PEGs as used with Adagen and Oncaspar, and a very limited number of larger more specific PEGs used with PegIntron and Pegasys, accompanied by subsequent improvements in linker chemistries, provided the foundational strategies for the products that followed. A summary of key approved products is presented in Table 1.

NOTABLE APPROVALS

In addition to the aforementioned four pioneer products, several PEGylated products deserve a mention.

Amgen's Neulasta (pegfilgrastim), a recombinant human granulocyte colony-stimulating factor (GCSF) analog for the treatment of neutropenia, involves the attachment of a single linear 20-kDa PEG to

the N-terminus position of the glycoprotein using a novel aldehyde alkylation strategy.

Eyetech's (Bausch) Macugen (pegaptanib), an anti-angiogenic oligonucleotide for the treatment of neovascular (wet) age-related macular degeneration (AMD), represents the only approval to date of a PEGylated aptamer. PEGylation involves attachment of a single branched 40 kDa to an amine at the 5′ end of the aptamer. PEGylation provides the necessary protection from serum nucleases to extend the half-life of this sensitive molecule.

UCB's Cimzia (certolizumab pegol), a tumor necrosis factor alpha for the treatment of a variety arthritic-related conditions, represents the first, and to date, only use of PEGylation to extend the duration of action of an antibody fragment. The product features an engineered thiol that permits selective attachment of a 40kDa branched PEG.

Affymax's Omontys (peginesatide), a functional analog of erythropoietin for the treatment of anemia, is still the only peptide to be approved using PEGylation. Omontys used a unique 40-kDa branched PEG linker to connect the two separate peptides

TABLE 1

Product	Originator Company	First Approval	Molecular Weight (kDa)	Molecule Type	PEG Size (kDa)	PEG Number	PEG Geometry	Key Benefit
Adagen (pegadamase)	Enzon	1990 (US)	96-126	Enzyme	5	11-17	Linear	Reduced Immunogenicity
Oncaspar (pegaspergase)	Enzon	1994 (US)	483-548 (tetramer)	Enzyme	5	69-82	Linear	Reduced Immunogenicity
Peg-Intron (PEG-interferon alpha 2b)	Schering-Plough	2000 (Canada)	31	Protein	12	1	Linear	Duration of Action
Pegasys (peginterferon alfa-2a)	Roche	2001 (Switzerland)	60	Protein	40	1	Branched	Duration of Action
Somavert (pegvisomant)	Sensus	2002 (EU)	42-52	Protein	5	4-6	Linear	Enhanced Stability, Duration of Action
Neulasta (pegfilgrastim)	Amgen	2002 (US)	39	Glycoprotein	20	1	Linear	Duration of Action
Macugen (pegaptanib)	Eyetech	2004 (US)	50	RNA Aptamer	40	1	Branched	Enhanced Stability, Duration of Action
Mircera (Peg-erythropoietin beta)	Roche	2007 (EU)	60	Cytokine	30	1	Linear	Duration of Action
Cimzia (certolizumab pegol)	UCB	2008 (US)	91	Antibody Fragment	40	1	Branched	Enhanced Stability, Duration of Action
Omontys (peginesatide)	Affymax	2012 (US)	45	Peptide	40	1	Branched	Enhanced Stability, Duration of Action
Movantik (naloxegol oxalate)	Nektar	2014 (US)	0.65	Small Molecule	0.4	1	Linear	Limit CNS Exposure
Plegridy (peginterferon beta-1)	Biogen	2014 (EU)	44	Protein	20	1	Linear	Duration of Action
Jintrolong (pegylated recombinant human growth hormone)	GeneScience	2014 (China)	62 (estimated)	Protein	40	1	Branched	Duration of Action
Rebinyn (nonacog beta pegol)	Novo Nordisk	2017 (US)	98	Protein	40	1	Branched	Duration of Action
Palynziq (pegvaliase)	BioMarin	2018 (US)	250 (monomer)	Enzyme	20	9	Linear	Reduced Immunogenicity
Jivi (damoctocog alfa pegol)	Bayer	2018 (US)	234	Protein	60	1	Branched	Duration of Action
Revcovi (elapegademase)	Leadiant	2018 (US)	113	Enzyme	5.6	13	Linear	Reduced Immunogenicity, Enhanced Stability
Asparlas (calaspargase pegol)	Servier	2018 (US)	313 (tetramer)	Enzyme	5	31-39	Linear	Reduced Immunogenicity, Enhanced Stability
Esperoct (turoctocog alfa pegol)	Novo Nordisk	2019 (US)	216	Protein	40	1	Branched	Duration of Action
Besremi (ropeginterferon alfa-2b)	PharmaEssentia	2019 (EU)	60	Protein	40	1	Branched	Duration of Action, Improved Safety

Key PEG Product Approvals (1990-August 2020). **Source: PharmaCircle Pipeline & Products Intelligence Module**

of the dimer.[2] The product was recalled from the market in 2013, within a year of approval, because of hypersensitivity issues, and formally withdrawn in 2019.

Nektar's Movantik (naloxegol oxalate), an opioid antagonist for the treatment of opioid-induced constipation, represents the only approved PEGylated small molecule. The therapeutic strategy of using the PEG, in this case a 400-Da (7-mer), is to increase the hydrodynamic size of the molecule, limiting passage across the Blood Brain Barrier, while still antagonizing opioid binding in peripheral tissue. The PEG is connected through an ether linkage to the 6-α-hydroxyl.

REDOS

Two recently approved products, Leadiant's (Sigma-Tau) Revcovi (elapegademase) and Servier's Asparlas (Calaspargase pegol) are notable in that they represent "redos" of the first two approved PEGylated products, Adagen and Oncaspar, respectively. A quick look at Table 1 reveals that they basically use the same PEGylation approaches with the same therapeutic objectives as their precursors; non-specific PEGylation with 5-kDa PEG. The difference is the PEG linker used. The two earlier products both used SS-PEG, succinimidyl succinate PEG, which produced an ester linkage between the PEG conjugate and enzyme that was sensitive to hydrolysis. In contrast, Revcovi and Asparlas both use SC-PEG reagents, succinimidyl carbonate PEG, that produce a more stable connection without the ester linkage. In the case of Asparlas, this has also resulted in a longer duration of action.[4]

While not a "redo" as such, PharmaEssentia's Besremi (ropeginterferon alfa-2b) combines interferon alpha 2b, the native protein in Schering-Plough's PegIntron, with the PEGylation strategy of Roche's Pegasys, a 40-kDa branched PEG. Approved by the EMA in 2018, the product is indicated for the treatment of Polycythemia Vera rather than the original Hepatitis C indications of PegIntron and Pegasys.

NOTABLE MISSES

A number of PEGylated products did not make it through to approval, a few of them using a novel chemical or therapeutic strategy that are worth understanding.

In the early 2000s, Enzon undertook the development of a pair of PEGylated small molecule antineoplastic drugs using releasable linkers. The concept was that these molecules, chemotherapeutics linked to either end of a bifunctional PEG molecule, would be preferentially taken up by tumor cells and, when released in the tumor, exert selective cytotoxicity. These larger molecules would also be less subject to kidney filtering and excretion, extending duration of action. The results with both camptothecin (Pegamotecan) and paclitaxel (Peg-Paclitaxel), which went as far as Phase 2 trials, were unconvincing. Beyond the failure to provide any type of clinical benefit, there were formulation concerns as these products used 40-kDa bifunctional PEGs. This resulted in very large molecules that carried only two actives but increased the overall product mass about 50-fold. This suggested a very large dosage form that might have led to issues related to the accumulation of these 40-kDa-released PEGs. The development of these products was quietly discontinued. Since then, the suggestion has been made that this strategy might be feasible with the use of multi-arm PEG molecules.

An interesting small molecule PEGylation strategy that was terminated for business rather than clinical reasons was Nektar's Kyvoda (oxycodegol), an opioid analgesic with designed abuse-deterrent properties. The product was a 6-mer PEG molecule conjugated through an ether linkage to the 6-α-hydroxyl of a reduced analog of oxycodone. The addition of the PEG was intended to slow, but not prevent, the central uptake of the analgesic and limit its abuse potential. While the product was shown effective and safe in clinical trials, it was rejected by an FDA advisory committee at a time when all opioids, regardless of abuse- deterrent potential, were under very close scrutiny. Nektar chose to withdraw the product's application with the FDA rather than continuing to advance into regulatory headwinds.

THE CURRENT PEG PIPELINE

A review of the PharmaCircle Pipeline & Products Intelligence module reveals a total of 49 PEGylated products at some stage of registration or clinical development. This includes three products filed for approval, 12 in Phase 3, 20 in Phase 2, and 14 in Phase 1. It would be an understatement to say the pipeline is robust. These products represent both innovative products and biosimilars. Among this four dozen or so products are two that embody interesting PEGylation or therapeutic strategies.

ACP-001 (lonapegsomatropin), currently in registration in the US, uses Ascendis Pharma's TransCon technology to

conjugate a 40-kDa PEG with human Growth Hormone (hGH) and release the fully active native hGH. The effect is an extended circulating half-life that permits dosing once per week versus the usual once a day for hGH.

Molecular Partners' and Allergan's (AbbVie) DARPin (abicipar pegol) is an anti-VEGF protein filed for approval with the FDA for the treatment of neovascular (wet) age-related macular degeneration. It is a 34-kDa molecule composed of a 14-kDa recombinant protein and a 20-kDa PEG. Intended for administration intravitreally every 2 to 3 months, the product recently received a Complete Response Letter from the FDA related to safety issues.

PEG REAGENT SUPPLY & SUPPLIERS

There was a point some 20 years ago that the supply of monodispersed PEG reagents was severely constrained as a result of patents, restrictive licensing supply agreements, and a single supplier of the unactivated PEG polymers. A cross license between Enzon and Nektar largely resolved the patent issues for each company's clients.[1] With basic PEG patents expiring over the next decade, the field was opened to new competitors. The result has been further innovation and a robust pipeline of products and product approvals. A quick search of PharmaCircle's CMO/CRO database identified no less than 31 companies offering PEG reagents in a wide variety of sizes, geometries, and activation chemistries.

WHAT'S NEXT FOR PEGYLATION?

After 30 years of drug approvals and a full pipeline, there is little question that PEGylation will be relevant for at least the next decade. Was PEGylation fortunate that's its birth coincided with the emergence of macromolecule therapeutics? Or was the field of macromolecules fortunate that PEGylation arrived when it did?

Newer conjugation approaches promising comparable benefits are yet to deliver product approvals. Any new technology will face a difficult business environment. The economics of PEGylation started to shift in the late 1990s as Enzon's foundational PEGylation patents were approaching their end of life and Shearwater was offering attractive technologies with more competitive pricing. There are no longer any pesky licensing fees required to use PEGylation. All that is needed is the supply of a suitable PEG reagent and the necessary know-how.

When technology becomes open source, it often leads to limited investment and innovation because there is little motivation to invest without intellectual property protection. PEGylation has flourished for the past decade as an open source technology. Will this continue or will openness actually stifle the development of next-generation PEGylation technologies? Let's see where PEGylation is a decade from now.◆

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PLATFORM TECHNOLOGY

Morphomer™ & SupraAntigen™ Platforms: Targeting Misfolded Proteins in Neurodegenerative Disorders

By: Andrea Pfeifer, PhD

INTRODUCTION

Neurodegenerative diseases are an ongoing public health crisis, with the two most common, Alzheimer's disease and Parkinson's disease, affecting more than 55 million patients worldwide.[1-3] Marketed therapies for these debilitating disorders provide only temporary relief from symptoms leaving patients and their caregivers to cope with disease progression and society bearing the tremendous socioeconomic costs associated with medical care and lost productivity.[4,5] Advanced forms of neurodegenerative diseases are particularly challenging to treat; indeed, using current diagnostic technologies, it may already be too late to intervene at the time of diagnosis.[6] Thus, an urgent need exists for new technologies that can detect pre-symptomatic neurodegenerative disease, as well as novel disease-modifying treatments that can halt or reverse disease progression.

Protein misfolding and aggregation within and around neurons is a major hallmark of neurodegenerative diseases.[7] Proteins that normally carry out essential functions in the healthy brain undergo changes in their three-dimensional structures resulting in abnormal conformations that can alter or completely disrupt protein functions. For example, changes in three-dimensional protein structure may lead to rearrangement of hydrogen bonding sites and an increased tendency for misfolded proteins to aggregate into specific oligomers, forming β-sheets. Pathological changes to three-dimensional protein structure, proteinopathies, in the brain can be caused by various events, such as genetic mutations and oxidative stress, but in most cases, the specific mechanisms underlying changes in protein structure remain poorly understood.

Each neurodegenerative disease has a specific hallmark protein (or set of proteins) that undergoes structural changes and assembles into insoluble aggregates. In Alzheimer's disease, amyloid-beta and the protein Tau form amyloid plaques and neurofibrillary tangles, respectively; whereas, in Parkinson's disease, alpha-synuclein accumulates and generates cellular inclusions known as Lewy bodies. Depending on the protein, these toxic aggregates can accumulate inside neurons or in the extracellular space and ultimately cause irreversible damage to neurons.

Misfolded proteins in the extracellular space may also drive the progression of neurodegenerative disease through the induction of seeding, a process by which misfolded proteins drive the spread of protein aggregates throughout the brain by inducing the misfolding of protein molecules still in their naïve state. Further, interactions between different protein species can lead to cross-seeding events and the existence of co-pathologies. For example, people with advanced stages of Alzheimer's exhibit aggregation of not only Tau and amyloid-beta, but are also more likely to harbor misfolded variants of other proteins, such as alpha-synuclein or TAR DNA-binding protein 43 (TDP-43).[8,9]

The complex aggregation and interactions of the many protein species involved in neurodegenerative diseases have motivated the pursuit of precision and combination medicine approaches to target the right protein at the right time. To drive the development of such therapies, therapeutic and diagnostic tools targeting a broad array of proteins are needed. Moreover, tools should specifically target aggregated forms of the relevant proteins or their pathological precursors, as less-specific targeting of all forms, including the "normal" form, of a protein may disrupt critical biological functions. The development of these tools may

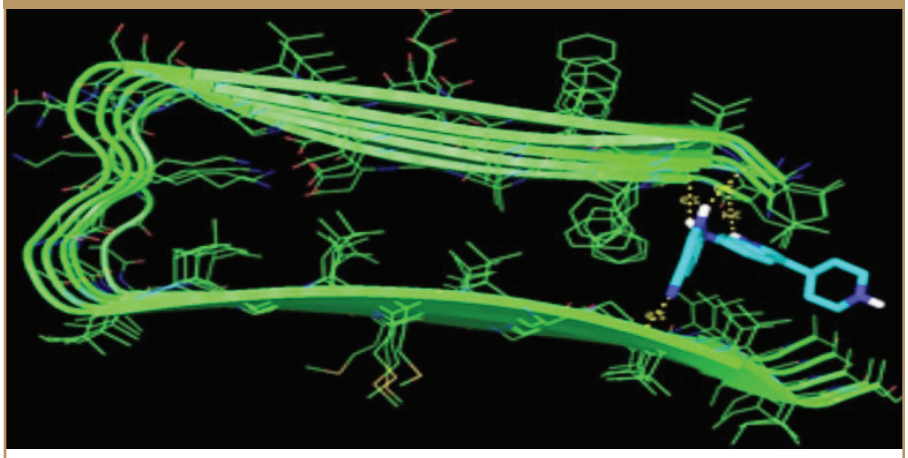
enable the detection of misfolded proteins before clinical symptoms are evident and the prevention of the neurodegeneration that leads to cognitive or motor impairment.

As well as the usual challenges of drug development, there are challenges specific to the development of agents designed to target proteins of the central nervous system (CNS). CNS-targeting therapies and diagnostics must distinguish between normal and toxic forms of the same proteins that differ only by their spatial conformation, a substantial challenge that the body's natural innate immune system cannot meet. Further, such targeting agents must have an ability to cross the highly impermeable blood-brain-barrier, while, at the same time, maintaining a favorable safety and tolerability profile.

Here, we detail the efforts of AC Immune, a Swiss-based, clinical-stage biopharmaceutical company with a broad pipeline focused on neurodegenerative diseases, to develop the therapeutic and diagnostic tools necessary to enable precision medicine approaches targeting the right protein, at the right time, in the right patient. AC Immune's industry-leading pipeline includes a broad array of conformation-specific antibodies, vaccines, and small molecules directed against misfolded and pathological forms of both well established (eg, Tau and amyloid-beta) and novel (eg, TDP-43) targets in neurodegenerative diseases.

The pipeline is powered by the company's two proprietary drug development platforms, SupraAntigen™ and Morphomer™. Together, these platforms accelerate the design, development, and validation of highly selective small molecules, antibodies, and vaccines for therapeutic and diagnostic applications. These platforms are complementary and have been optimized specifically to overcome the challenges of developing therapeutic or diagnostic candidates for CNS proteinopathies.

FIGURE 1



Morphomers (blue) are conformation-specific, non peptidic, small molecules designed to specifically recognize pathological misfolded and β-sheet-rich aggregated protein forms (green). Morphomers show drug-like properties, including brain penetration, and can enter cells to access intracellular deposits of aggregated proteins.

THE MORPHOMER™ PLATFORM

Morphomer is a platform designed to enable the development of small molecules (Morphomers) able to bind/interact with β-sheet containing fibrillary aggregates from candidate selection through preclinical proof-of-concept. Morphomers (Figure 1) can target pathological protein aggregates in any brain compartment and are equally well suited for therapeutic and diagnostic applications.

The first key component of the Morphomer platform is its library of rationally designed, CNS-optimized non-dye compounds. AC Immune's extensive know-how has enabled the identification of CNS compounds that penetrate the brain and demonstrate selectivity for the target. This knowledge has been used to focus the Morphomer library to approximatively 10,000 compounds that display these favorable characteristics, making this library an ideal starting point when developing molecules to target human proteinopathies of the CNS. Thus, rather than using the non-directed trial-and-error strategy of the typical drug development process, the Morphomer platform utilizes its bias for successful CNS candidates to improve efficiency and accelerate the early stages of the drug development process.

Following the identification of initial hits from the Morphomer library, promising compounds undergo several rounds of iterative medicinal chemistry hit-to-lead optimization. A thorough testing process highlighted by AC Immune's proprietary suite of quantitative and qualitative selection assays provides the required feedback for continued compound optimization. These assays are designed to identify the hits showing *in vitro* activity against selected targets. The different assays are designed to provide detailed insights into one specific component of the molecule's target mechanism of action and allows the ranking of compounds according to their performance. Such ranking is useful both for the identification of potential lead com-

pounds, and to further refine the original CNS-biased compound library for future applications. Compared to typical drug development assays, AC Immune's assays expedite the lead selection process by reducing false positives, and ultimately more accurately identify compounds likely to specifically bind selected targets *in vivo*.

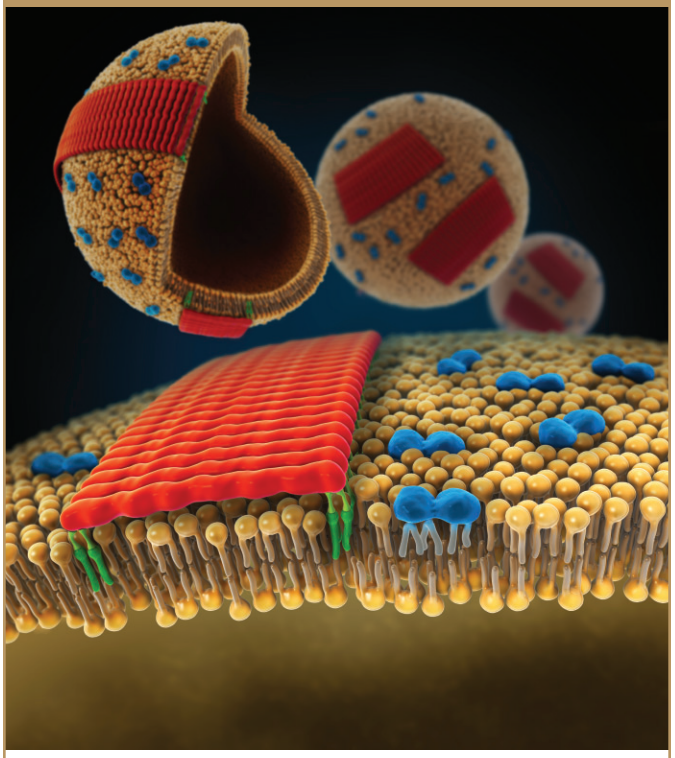
Once identified as a lead compound, the candidate then moves into the next phase of proof-of-concept testing. While no animal model can fully reflect the complexity of a human neurodegenerative disease, AC Immune has developed or gained access to a large collection of rigorously validated, relevant translational animal models to systematically evaluate a candidate's effect on the individual processes of human disease. Understanding how a small molecule targets pathological protein aggregates, if it prevents seeding rather than spreading: each feature can be determined through the application of a specific state-of-the-art assay to AC Immune's highly translational animal models.

The Morphomer platform has grown into an invaluable asset that has contributed to the development of AC Immune's industry-leading clinical pipeline for neurodegenerative diseases. Today, it stores years of research resulting in a detailed mechanistic understanding of the interactions of small molecules with an ever-increasing number of hallmark proteins implicated in neurodegenerative diseases. It provides a painstakingly optimized array of assays and compounds to further expand this expertise and accelerate the progression of small molecules through the drug development process. The platform has generated PI-2620, a Tau-positron emission tomography (PET)-tracer in Phase 2 development in partnership with Life Molecular Imaging, and ACI-3024, a small molecule Tau inhibitor in Phase 1 testing under a partnership with Eli Lilly and Company. Most importantly, it offers a strong foundation to continue to create the next generation of small molecules addressing novel targets with increasing efficiency.

THE SUPRAANTIGEN™ PLATFORM

SupraAntigen is a liposome-based technology platform developed to generate biologicals for immunotherapy. It was first developed by AC Immune's scientific co-founders for applications in oncology to overcome a challenge common to both cancer and neurodegenerative diseases: the lack of immunogenicity of disease-causing self-proteins. The SupraAntigen platform uses liposomes (small spherical vesicles formed by a lipid bilayer, as shown in Figure 2), to present specific antigens designed to evoke an immune response and generate antigen-targeting antibodies.

FIGURE 2



The SupraAntigen platform targets misfolded proteins through antigens (red) displayed on the surface of liposomes. These peptides, which mimic the targeted pathological form of the protein, are attached to the liposomal bilayer (yellow) using liposomal anchors (green) and presented together with the adjuvant (blue).

SupraAntigen is used to generate conformation-specific antibodies for immunotherapy in neurodegenerative diseases.[10] The overarching idea behind the platform is that antibodies, which are large in size, are well-suited to target extracellular proteins, interrupt spreading of pathological proteins, and break up and clear aggregates of misfolded proteins through phagocytosis.

AC Immune is the first and only company that has acquired advanced mastery of the design and manipulation of liposomes to develop either passive or active immunization techniques to generate antibodies targeting neurodegenerative diseases. When pursuing active immunization approaches, AC Immune uses liposomes carrying a specific antigen as a vaccine. After vaccination with a liposome, antigen and confirmation-specific antibodies are produced naturally by the host with very high affinity without further optimization. This immune response can be long-lasting and may be ideal to prevent the onset of a disease, as the immune system is now primed to rapidly identify disease-causing mis-

folded proteins.

To develop passive immunization strategies, AC Immune relies on the generation of antibodies, for example by injecting liposome constructs in mice, adapting them to the human immune system, and finally administering them to the patient to promote clearance of misfolded proteins. While passive immunization relies on frequent administration of exogenous antibodies, the "external" generation offers the opportunity to optimize antibodies for specific properties, which can prove critical when the patient's immune system is not capable of producing the desired antibodies on its own.

AC Immune is pioneering the liposome approach in CNS-targeted immunotherapy and has gained unique experience when it comes to engineering peptides, adjuvants, and liposomes. Such experience has facilitated the development of an approach that is superior to standard liposome-based techniques. While early liposome work suggested a length limitation of 15-50 amino acids for single peptides attached on a liposome, AC Immune's liposome technologies can incorporate several short peptides or whole proteins, enabling larger yield of antibodies and antibodies targeting a broad range of epitopes and epitopes with post-translational modification.

A critical aspect of AC Immune's liposome-based technology is its ability to generate antibodies that are specific for precise protein conformations, as the misfolded proteins that are the hallmark of neurodegenerative disease differ from self-proteins only by their conformational state. This tour de force is achieved by precisely controlling and stabilizing the spatial arrangement of the peptides on the surface of the liposome, allowing peptides to be presented to the immune system in a conformation-specific configuration. Arranging peptides in repetitive arrays can simulate aggregates and generate antibodies that recognize pathologic self-proteins as foreign. Excitingly, it is now possible to specifically induce a β-sheet conformation of peptides on the surface of the liposome.[11]

As AC Immune's liposome approach creates a range of antibodies against a specified target, it allows for the selection of those antibodies with the highest affinity and selectivity. When pursuing passive immunization techniques, AC Immune aims to select an antibody candidate that combines high affinity and high specificity for the target, as this enables a favorable safety and tolerability profile. Compared to typically employed antibody selection approaches, AC Immune employs an accelerated process by utilizing an extensive collection of specific proprietary assays. These assays are comparable to the proprietary assay suite used in the Morphomer platform, and have been designed and implemented by AC Immune to expedite the drug development process in a similar manner.

SupraAntigen has generated numerous anti-Tau and anti-Abeta antibodies such as crenezumab, currently in Phase 2 testing in partnership with Genentech, a member of the Roche group. ACI-35.030, an anti-phosphoTau vaccine in Phase 1b/2a development and partnered with Janssen Pharmaceuticals, was also developed using the platform.

Similar to Morphomers, the development of potential lead antibodies is accelerated by access to AC Immune's previously described bank of human brain tissue from patients with neurodegenerative diseases. Once *in vitro* activity target engagement with human tissue has been established, an antibody candidate is further validated in AC Immune's collection of relevant translational animal models. As with Morphomer, the SupraAntigen platform is much more than a technique by which to generate candidate vaccines and antibodies, as it accelerates the drug development process from its initial stages through preclinical proof-of-concept and validation in human tissue.

CLINICAL & EXTERNAL VALIDATION

The AC Immune platforms are the foundation of a pipeline that includes nine therapeutic and three diagnostic candidates, with six being actively studied in clinical trials. Candidates target a broad array of pathological proteins, including classical hallmarks of Alzheimer's disease, such as amyloid-beta and Tau, as well as novel targets, such as alpha-synuclein and TDP-43.

The power of the Morphomer and SupraAntigen platforms can also be seen when focusing on a single target, such as Tau. AC Immune has advanced four Tau-targeting assets into the clinic, including the anti-phosphoTau vaccine ACI-35.030, Morphomer Tau small molecule aggregation inhibitor ACI-3024, anti-Tau monoclonal antibody semorinemab, and Tau-PET-tracer PI-2620. Further highlighting the truly comprehensive approach the company is taking against this high-value target, several of these assets are first-in-class with all having best-in-class potential in a highly competitive race to bring Tau-targeting therapeutics and diagnostics to patients.

The immense value of the Morphomer

and SupraAntigen platforms is validated not only by the exciting preclinical and clinical data generated to date, but also by AC Immune's partnerships with leading global pharmaceutical companies, including Genentech, Janssen, and Lilly, all of whom have maintained long-standing dominant positions in development and sales of CNS therapeutics. These partnerships have already generated significant revenue for AC Immune, more than the company has raised from investors, without including potential milestones and royalties. In summary, these platforms are remarkable from both the scientific and business perspective, and their productivity will only increase as AC Immune continues to accumulate knowledge and adapt to the discovery of novel targets in proteinopathies, paving the way for precision medicine in neurodegeneration. ◆

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BIOGRAPHY

Prof. Andrea Pfeifer co-founded AC Immune in 2003, where she holds since foundation the position of CEO. Prior to AC Immune, she was head of Nestlé's Global Research in Lausanne, Switzerland, and managed a group of more than 600 people. While at Nestlé, she led the scientific development of the first Functional Food, LC1, and one of the first Cosmoceutical products in a joint venture with L'Oreal, Innéov Fermeté. She also co-founded the Nestlé Venture Capital Fund, a €100Mio. Life Sciences corporate venture fund. She serves as chairwoman of the Biotechmedinvest AG Investment Fund, Basel, and AB2Bio, Lausanne, and is member of the Supervisory Board of Symrise AG, Holzminden. Prof. Pfeifer is a member of the the CEOi Initiative on Alzheimer's disease. She was recognized in 2009 as Technology Pioneer by the WEF and Swiss Entrepreneur of the Year by Ernst&Young. Additional recognitions include the BioAlps prize 2013, the election as one of the top 10 women in biotech from Fierce Biotech, and one of the 300 most influential personalities in Switzerland. Prof. Pfeifer earned her PhD in Toxicology, Cancer Research from the University of Würzburg, Germany and continued with post-doctoral work in Molecular Carcinogenesis at the National Institutes of Health, Human Carcinogenesis Branch, in Bethesda, USA. She is a registered Toxicologist and Pharmacist, received her habilitation from the University of Lausanne, Switzerland, and is an honorary professor at the Ecole Polytechnique Fédérale de Lausanne, Switzerland. She has published more than 200 papers and abstracts in leading scientific journals.

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CDMO CASE STUDY

AJILITY: Streamlining Drug Product Manufacturing

By: Dustin Campbell

INTRODUCTION

In the current pandemic landscape, there is an increased focus on faster turnaround times. As drug developers race to get these critical therapies into the clinic and subsequently into commercial production, they are expediting the CDMO selection process along with tightening timelines for tech transfer, and the preparation and release process for fills.

Clinical timelines in general are usually very fast; and now, there is a stronger expectation that the CDMO can adjust quickly to meet the changing demands of the customers' programs.

There is also a large influx of government-sponsored and funded programs that are increasing the overall demand for capacity and intensifying the pressure on CDMOs to provide flexible, high-quality service that can meet the expectations of customers and the public. Demand for capacity is at an all-time high as clients look for fill and finish services for COVID-19 and Emergency Use Authorization (EUA) therapeutics, and CDMOs struggle alongside other industries to manage the changing landscape of doing business during the pandemic.

In response to this ever-evolving environment, it is more important than ever for CDMOs to ensure they are proactive with how they plan, resource, and execute programs with their customers; rather than reacting to the larger challenges they are facing with supply chain and general product development.

FIGURE 1

Ajinomoto Bio-Pharma Services' robust filling lines are designed to minimize product loss and offer a comprehensive range of vial batch sizes and vial size configurations.

While there has always a constant influx of drug products to the market, since the start of the pandemic, the speed and the number of vaccines, therapeutics, and candidates that have entered in clinical development has been extraordinary, making CDMOs and their capacity for manufacturing these products in high demand.

This past May, Ajinomoto Bio-Pharma Services announced two separate supply agreements with CytoDyn and with Humanigen to provide fill and finish manufacturing for their respective drug products, currently in clinical trials for COVID-19 patients.[1,2]

PROACTIVE PLANNING

The CDMO industry prides itself on its flexibility, adaptability, and responsiveness to changing customer needs. Helping drug developers address the challenges their programs may encounter, and adapting to their needs, is at the core of a successful CDMO business model.

Can CDMOs be more flexible? Offer more adaptive solutions? Provide more responsive services? How can customers get their life-saving treatments to the clinic faster? Those were the questions that Ajinomoto Bio-Pharma Services asked itself as the pandemic continued to spread.

In response to those questions and the changing landscape, the AJILITY™ platform was established.[3] The notable advantage of

the AJILITY platform is the ability for clients to leverage Ajinomoto Bio-Pharma Services' extensive experience in drug product manufacturing, technical knowledge, and regulatory support expertise to expedite therapeutics to the clinic, while maintaining the highest of quality standards.

Fundamentally, the AJILITY Platform takes the burden off the client and allows Ajinomoto Bio-Pharma Services to drive, manage, and support clients' drug product manufacturing, maximizing speed and success, and gives our clients peace of mind to partner with a CDMO that will prioritize these programs and drive them to completion.

AJILITY PLATFORM

In considering and developing the AJILITY platform, the Ajinomoto Bio-Pharma Services team worked through every step and aspect of the manufacturing process to define this service offering in order to provide a high level of support, ensuring a successful tech transfer or design of the clinical program from start to finish.[4]

There are some program details that tend to have a bigger impact on the timeline for tech transfer to a CDMO than others. Often, clients rely on input from consultants or historical precedent to dictate program decisions on things from components and method qualification to excipients and more.[4]

With AJILITY, the Ajinomoto Bio-Pharma Services team provides their experience to select and recommend a fast-tracking program that introduces fewer variables, speeding up the program timeline and minimizing the need for third-party support. Clients are able to select from in stock, preferred components and excipients from a long list of Ajinomoto Bio-Pharma Services GMP qualified vendors, rely on Ajinomoto Bio-Pharma Services personnel to set formulation details, fill tolerances and inspection-ready criteria based on expertise, and participate in an expedited review of methods and discussion/consultations as part of the proposal generation process.

FIGURE 2

Pre-filled syringe manufacturing services, including parenteral manufacturing, on high-speed pre-filled syringe line, using Restricted Barrier Access (RAB).

During the tech transfer and manufacturing process, Ajinomoto Bio-Pharma Services works with quality in mind, incorporating additional flexibility into the process by performing compendial methods verifications in parallel with manufacturing activities, and working concurrently on batch documentation reviewing to support a quick release. Performing risk assessments early in clinical development is another tactic customers use to fast track the clinical process and expedite the path to filing. Release timelines are often subject to great variability based on issues that arise during the manufacturing process. Deviations result in investigations that can significantly impact the timeline for release. Working with an experienced CDMO can leverage know-how on the front end to save headaches on the back end.

Clients also benefit from remote site auditing. Current travel restrictions and concerns are making the standard in-person audit difficult, and the compliance team at Ajinomoto Bio-Pharma Services has developed a virtual and online site visit and audit experience to ensure customers are meeting their quality obligations for selecting or maintaining a qualified vendor. Through the use of the portal systems and virtual site tours, clients can be assured they will be able to perform a thorough review of the facilities and quality systems and have connections with the subject matter experts to meet their program requirements and quality standards. Other efficient tools for speeding up time to release include working from templated batch documentation to quickly generate a Master Batch Record (MBR), utilizing an existing library of packaging and labeling components, and employing existing validated shipping configurations and preferred couriers.

The Ajinomoto Bio-Pharma Services regulatory team provides guidance with e-submissions and EUAs, discussing your program needs and working with regulatory agencies to tailor procedures to your program. Ajinomoto Bio-Pharma Services has a long history of working with the FDA on

FIGURE 3

Ajinomoto Bio-Pharma Services uses dedicated system technology with integrated fill line and lyophilization unit for filling highly potent compounds, including ADCs.

these types of submissions and is uniquely qualified to support these types of programs be it for COVID or other indications.

FOCUSED TECH TRANSFER

Tech transfer activities for bringing a new product or process into the facility are usually rate-limited by analytical method transfers, availability of components, and formulation specifics. Especially in early stage novel therapeutics, there are often gaps between the state of the methods for in-process control and product analysis and what is suitable for cGMP operations.

Likewise, with the formulation process, these early stage programs have been performed on a bench top with inadequate attention having been paid to the scale and process characterization needed to ensure a successful cGMP operation. Many times this is an education process between both the customer and the CDMO, with the rate-limiting terms needing clarification to be in place prior to a run. A clinical-to-commercial program typically involves fewer unknowns, but includes long lead time activities that may or may not propose a risk to a customer's timeline depending on the quality of the process characterization activities that the customer and CDMO focused on during clinical development.

With the AJILITY platform, leveraging Ajinomoto Bio-Pharma Services' experience to ensure the best fit for the product and the facilities, the time to manufacturing is greatly reduced, and many of the challenges that typically occur can be planned for or altogether avoided. Qualifying and transferring a product to a new CDMO can be a stressful and difficult ordeal for clients, and the AJILITY platform is a key resource for getting patients the therapeutics they need. Late-stage development also has time and cost hurdles that can be circumvented by designing these early stage programs in such a way as to leverage as much information as possible in late-stage and decrease the scope of work needed to get from clinical to commercial scale.

TAILORED DRUG PRODUCT MANUFACTURING

Once tech transfer activities are finalized, drug product manufacturing can bring its own challenges to work through, from batch record completion and engineering studies to fill line availability, which individually and together can traditionally slow programs down.

To overcome these hurdles and reduce variables, the AJILITY platform offers several areas to gain time-savings. For example, there is the potential to skip engineering studies prior to cGMP operations (dependent on the product), using the existing library of mixing and product contact parts to minimize compatibility studies, and fill line flexibility allows clients to benefit from capacity availability. Ajinomoto Bio-Pharma Services has multiple filling lines for all standard formats, including vials, syringes, and cartridges. Taking advantage of Ajinomoto Bio-Pharma Services' extensive experience in manufacturing a wide variety of drug products and working together on these program considerations can significantly cut down the manufacturing timeline.

ENSURED PRODUCT QUALITY

Well-designed product quality and analytical programs are critical to ensure a successful final product. Ajinomoto Bio-Pharma Services' on-site laboratories are equipped with sophisticated equipment, enabling our scientists to employ a full range of methodologies and techniques to characterize clients' products and develop test methods to validate a product's quality through its life cycle.

The AJILITY platform offers time-savings for analytical services while sustaining prod-

uct quality with concurrent and in parallel reviews and method verifications, minimized analytical transfer scope, and satellite ID samples for bulk drug substance lots sent back to the drug substance manufacturer to decrease the cost and time associated with method transfer.

EFFICIENT PACKAGING & SHIPPING

In order to support a product's clinical performance and market success, Ajinomoto Bio-Pharma Services offers in-house labeling and packaging solutions that provide greater safety and efficiency for your supply chain with our Drug Supply Chain Security Act compliant track and trace service. On-site storage and distribution services minimize supply chain risk inherent to third party sites and makes the supplier management process simpler for our clients

Customers using the AJILITY platform are able to choose from an existing library of packaging and labeling components, use validated shipping configurations and preferred couriers and allow Ajinomoto Bio-Pharma Services personnel to schedule the shipments, and have drug product lots shipped, often under quarantine if the situation permits. Shipping is one less thing clients need to worry about with the AJILITY platform.

AGILE REGULATORY SERVICES

Ajinomoto Bio-Pharma Services has a long history of partnering with our clients on unique programs that require prompt attention and a strong regulatory strategy. Our agile regulatory team works to expedite processes allowing us to manufacture your product faster with process performance qualification and commercial manufacturing in mind.

Collaborating with a regulatory service group that has expertise in EUA product requirements, has an established e-submission policy with the FDA, a CMC section authoring program, concurrent batch documentation review, and can advocate for your program with regulatory agencies and provide the guidance and support to get your therapeutic reviewed and approved quickly and efficiently.

Using the AJILITY platform, Ajinomoto Bio-Pharma Services' regulatory team is available to assist with and has contributed to numerous clinical and marketing application submissions, and is ready to help with your regulatory submissions, clinical filings, and commercial launches. Clients need a team that has the experience and insight to help navigate any obstacles and progress these critical vaccines and therapies to clinics.

REMOTE ACCESS MONITORING

The ability to observe the manufacturing process is something that varies among CDMOs. Ajinomoto Bio-Pharma Services offers a personalized, secure, and remote viewing platform for clients to monitor their filling process through our ClientConnect™ portal. This provides the clients with the ability to monitor the operations in real time and to stay connected to their product even when they cannot be physically present.

Ajinomoto Bio-Pharma Services remote auditing procedures additionally provide clients with technology platforms to support live, interactive conversation/interviews, guided walk-through of operational areas, and the ability to review documents and data.

DESIGNED FOR SPEED

While the pandemic has presented a unique opportunity for our customers to capitalize on Ajinomoto Bio-Pharma Services' regulatory and manufacturing expertise through our AJILITY integrated drug product manufacturing platform, the AJILITY program will be available beyond the pandemic for any therapeutic program that needs flexible and responsive support for expediting your life-saving therapeutic to the clinic. With AJILITY, clients can move from signature to filling in as little as 6 weeks. For more information about the AJILITY platform, visit AjiBio-Pharma.com/AJILITY. ◆

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BIOGRAPHY

Dustin Campbell is the Associate Director of Commercial Operations at Ajinomoto Bio-Pharma Services, a global CDMO that specializes in a wide variety of manufacturing services supporting the Bio-Pharmaceutical and Small Molecule manufacturing industry. Mr. Campbell has a degree in Molecular Biology from the University of California San Diego and fifteen years industry experience working in Drug Substance and Drug Product manufacturing, Technology Transfer and Project Management.

DRUG DELIVERY

Recognizing the Patient Potential for Transdermal Drug Delivery

By: Sally Waterman, PhD and Vasiliki Nikolaou, PhD

THE IMPORTANCE OF CONSIDERING DELIVERY IN DRUG DEVELOPMENT

Developing drugs to successfully treat life-altering diseases is a daunting and challenging task. Not only do researchers have to identify an active compound, but it must also be delivered to the target site without being broken down or causing severe side effects. It is therefore important that drug developers consider the best way to deliver a drug at the outset of the development process.

Traditional methods of drug delivery, such as oral or intravenous (IV), have limitations both in their effectiveness and their practicality. Oral delivery is generally considered to be the most desirable as tablets and capsules can be easily manufactured in very large numbers, and most patients are able to self-administer them. However, there are some drugs that are extensively metabolised when given by the oral route, limiting their bioavailability, and others that cause gastrointestinal (GI) side effects. It may also be difficult to avoid off-target side effects because of spikes in the amount of drug in the blood following each dose. The delivery of drugs by the IV route overcomes the problems associated with first-pass metabolism and GI side effects but has other practical implications. The product needs to be manufactured and packed under sterile conditions, and patients cannot self-administer their treatment. Injections can be painful, and some patients find the use of needles an unpleasant experience. IV delivery also produces spikes in the drug concentration in the blood, so side effects can still be a problem.

For conditions that are local, such as pain from an injury, topical drug delivery with creams, gels, and patches can avoid GI side effects and, because the products are designed to deliver drugs locally, reduce systemic levels and thereby the risk of serious side effects. When systemic delivery of the drug is required for it to be effective, sustained release from a transdermal product, such as a patch, can improve bioavailability by avoiding first-pass metabolism, and reduce side effects by delivering the drug gradually over an extended period. Extended delivery of the drug can also reduce the frequency of dosing relative to immediate-release oral or IV products, which helps improve patient compliance.

There are, however, some downsides to topical and transdermal treatments. The skin has evolved to be a highly effective barrier, protecting the body from external factors and preventing water from escaping. Drugs delivered through the skin must therefore have certain physicochemical properties to be able to pass through this barrier so not all are suitable for delivery via this route. One assessment of suitability is to determine whether the drug satisfies Lipinski's rule of 5: has a molecular weight of <500 Da, <5 hydrogen bond donors, <10 hydrogen bond acceptors and a partition coefficient (log P, lipophilicity measurement) of <5.[1]

If a drug has physicochemical properties that favor its delivery into or through the skin, a range of formulation options can be considered. Creams and gels can be easily washed or rubbed off and can deliver only a relatively small amount of drug at each application, so must be applied multiple times a day. In addition, dose control is difficult because of user variability in the amount that is applied. A patch is formulated with a defined amount of

drug, and assuming it sticks well to the skin, provides certainty over the dose. Patches can be formulated with higher amounts of drug than creams or gels so dosing is less frequent and extended delivery over multiple days may be possible. Patch formulations therefore have benefits over topical creams and gels.

GROWING POPULARITY OF PATCH PRODUCTS

Patches are well-established for treating motion sickness and for smoking cessation and have more recently been developed for localized pain relief, delivering drugs such as diclofenac and ibuprofen directly to the site of the pain, as well as for chronic conditions such as Alzheimer's disease, Parkinson's disease and schizophrenia. There is increased interest in transdermal delivery of drugs, and the patch market is predicted to grow at a rate of 4.2% between 2017 and 2025.[2]

There are several types of a drug delivery patches: matrix, reservoir, multi-laminate, and drug-in-adhesive. All have a multi-layered structure with a backing film, an adhesive for sticking the patch to the skin, and a protective release liner that is removed before the patch is applied. The drug and excipients are either combined with the adhesive or in a separate layer. Most of the patches used by the pharmaceutical industry are of reservoir/controlled-release membrane and drug-in-adhesive design.[3] Some patches are unsuitable for low-potency drugs because insufficient drug can be loaded into the patch to provide efficacious levels of drug in the blood. Other issues include insufficient adhesion to the skin, which could lead to reduced efficacy if the full dose is not delivered, and a poor patient experience with many patches being uncomfortable, painful to remove, or unattractive due to a black ring around the patch caused by "cold-flow" of the adhesive.

NEW TRANSDERMAL PATCHES IN DEVELOPMENT

Medherant is a transdermal drug delivery technology developer based in Coventry, UK. The company develops drug-in-adhesive patches using its unique TEPI Patch® technology. Its lead product is a patch formulation of an approved oral therapy for smoking cessation. This is a drug-in-adhesive formulation that uses a novel adhesive which overcomes many of the limitations of other patches currently on the market, including the following:

- The adhesive enables a higher payload (up to 50% wt) to be added so it can be used to formulate a wider range of less-potent drugs or to extend the duration of delivery of a drug. In addition, permeation enhancers can be added to improve penetration of the drug through the skin. The high drug loading capacity also means that smaller and thinner patches can be produced.

- The novel adhesive sticks to the skin very well, important for ensuring that the intended dose of the drug is delivered.

- The patch is painless to remove and does not leave a black ring on the skin, so it is more acceptable to users.

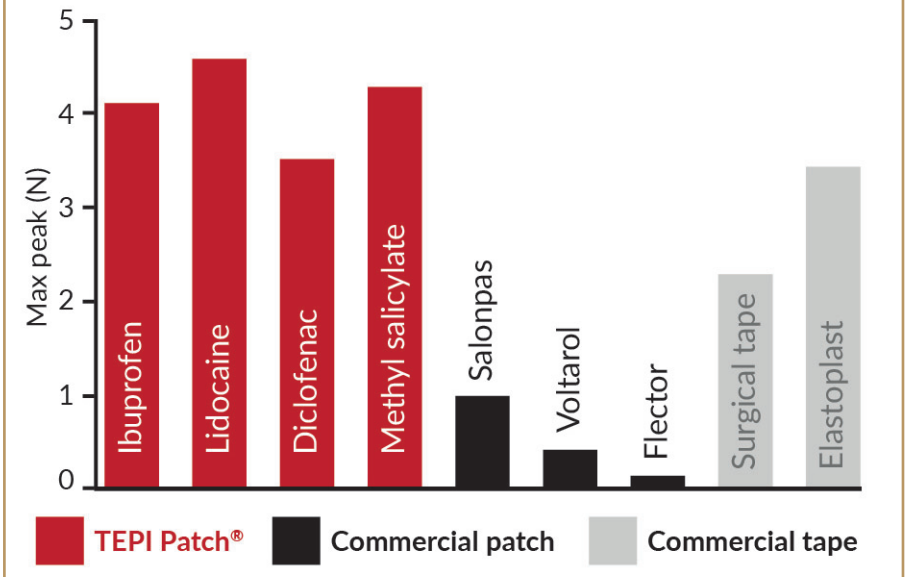
- Drugs are readily released from the adhesive leading to less residual drug in the patch on removal, important for its safe disposal.

ADVANTAGES OF TREATING ALZHEIMER'S DISEASE TRANSDERMALLY

Whilst localized pain relief is an obvious and growing market for transdermal drug delivery patches, there are many other diseases in which this technology offers distinct advantages. One such disease is Alzheimer's, the incidence of which is increasing as the proportion of elderly people in the population grows. Dementia, of which around 60% to 70% is due to Alzheimer's disease, is predicted to affect 152 million people worldwide by 2050, a 204% increase from 2018.[4,5] This will have a big impact, not only on the lives of those affected and their families, but also on health and social services. It is predicted that the cost of dementia in the UK will more than double in the next 25 years.[5] Alzheimer's disease is still relatively poorly understood, and drugs developed to date are only treating some of the symptoms, rather than preventing or curing the disease. It is important that we research ways to prevent it and slow its progression to lessen its impact, as well as developing and improving those treatments that already exist.

Oral dosing in Alzheimer's disease patients has its own specific problems. Dementia's main symptom is memory loss, so ensuring dose compliance is difficult as it is likely that the patient will forget to take their medication. A patch that delivers the prescribed drug dose over an extended period offers a potential solution to this issue, as well as reducing the risk of some side effects by avoiding exposure to the GI

FIGURE 1



Medherant's TEPI patch showed higher adhesion compared to commercially available patches and tapes using a standard *in vitro* method.

tract and eliminating the spikes in drug blood levels. In addition, elderly people are predisposed to develop dysphagia (difficulty swallowing) due to comorbid health conditions, and this can affect their ability to take oral medication.[6]

One of the few drugs already approved for the treatment of dementia in Alzheimer's disease is donepezil. Donepezil is an acetylcholinesterase inhibitor that prevents the neurotransmitter acetylcholine from being broken down. Acetylcholine is found in lower levels in brains affected by Alzheimer's. It is important for communication between nerve cells, so maintaining its levels is important for healthy brain function.[7] Donepezil is currently available as a tablet to be taken daily. Its side effects include nausea and vomiting.[8] Rivastigmine, an alternative acetylcholinesterase inhibitor used in Alzheimer's disease, is currently available as a patch formulation that delivers the drug over 24 hours.[9] The use of a patch to treat Alzheimer's has therefore been established. Donepezil is being developed as a patch formulation by several companies.

HOW CAN TRANSDERMAL PATCHES TREAT CHEMOTHERAPY-INDUCED NAUSEA & VOMITING?

As well as offering clear compliance benefits in Alzheimer's disease, transdermal patches can help deliver drugs in patient groups with other challenges associated with oral dosing. One such treatment area is chemotherapy-induced nausea and vomiting (CINV). This is a common problem for those going through chemotherapy, and it is hard to treat as it is difficult for patients to keep down any orally dosed medication. If the patient is unable to retain the oral dose, it will not be absorbed and therefore cannot treat the CINV effectively. IV dosing is not an attractive alternative as making patients stay in hospital longer around each dose of chemotherapy is both unappealing for the patient and costly for the healthcare provider. It is also important to consider that patients are more likely to miss a dose of chemotherapy or have their dose reduced if they suffer from CINV, so finding a solution is of utmost importance.

Patients with CINV often need to take more than one drug to reduce their symptoms. Providing patch formulations of these drugs would reduce their pill burden. The goal is to ensure patients can receive and retain the full dose of their drug to reduce nausea and vomiting so they feel well enough for their planned course of chemotherapy to proceed without dose reduction or missed doses. A patch formulation of granisetron is already available and a patch formulation of olanzapine, which is approved to treat schizophrenia and bipolar disorders[10] but is also used off-label to treat CINV, is in development for cancer patients being treated with poly ADP ribose polymerase (PARP) inhibitors. There is an opportunity to produce patch formulations of other drugs used to treat CINV, such as palonosetron, dexamethasone or rolapitant[11], to improve the quality of life of cancer patients.

HELPING PATIENTS BY RETHINKING DELIVERY

It is clear from these examples there are many diseases for which delivery route is an important factor that should be considered when treatments are being developed. Whilst the pharmaceutical industry has traditionally focussed on oral or IV delivery options, there are significant potential benefits of alternative methods of drug delivery for patients suffering from a range of diseases. It is therefore important the po-

tential benefits of other methods are considered, both for existing treatments to improve patient outcomes and experience, and for new treatments from the outset of the development process. Transdermal drug delivery patches have the potential to significantly improve not only the outcome of treatments but also the quality of life for those patients using them, the ultimate goal of any drug development professional. Working alongside a drug delivery specialist should therefore be essential for every drug developer. ◆

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BIOGRAPHIES

Sally Waterman joined Medherant in 2017 from Abzena plc, where she was Senior Vice President, Corporate Development. She initially joined its predecessor, PolyTherics Ltd, as COO, prior to its admission to AIM. She has over 30 years of strategic and operational experience, including leading R&D and extensive involvement in M&A, and has worked for large pharma, small biotech/biopharma, and contract service companies. She is also Chair of OBN Ltd.

Dr. Vasiliki Nikolaou has a strong foundation in polymer science, having devoted her academic career to polymer chemistry. Her PhD involved an industrial collaboration, which continued into her post-doctoral work at the University of Warwick and resulted in contributing to over 20 publications. She joined Medherant in 2016 and has a comprehensive knowledge of key industrial partners in the fields of polymer and organic chemistry.

Drug Development
EXECUTIVE

Daniel Vitt, PhD
CEO & President
Immunic Therapeutics

Immunic Therapeutics: Developing Next-Generation Oral Drugs in Chronic Inflammatory, Autoimmune & Infectious Diseases

Immunic Therapeutics is a global, clinical-stage biopharmaceutical company developing a pipeline of selective, small molecule therapies aimed at treating chronic inflammatory and autoimmune diseases, including relapsing-remitting multiple sclerosis, ulcerative colitis, Crohn's disease, and psoriasis. It is also testing its lead compound against COVID-19. Founded in 2016, the company rapidly created a risk-balanced pipeline of potentially best-in-class, orally available molecules comprising two compounds with attractive safety profiles and known targets, and one potentially disruptive technology, all focused on indications with high unmet need and significant market value.

Drug Development & Delivery recently interviewed Daniel Vitt, PhD, Immunic's Chief Executive Officer and President, to discuss the Company's pipeline and progress. Dr. Vitt was previously at 4SC, where he was a founder and also served as Chief Scientific and Chief Development Officer.

Q: What can you tell us about Immunic's progress over the past year?

A: Immunic began 2019 as a small, private company based in Germany with our lead program being in one clinical Phase 2 trial and two preclinical assets. Within the year, we had transformed into a Nasdaq-listed, public pharmaceutical company via a reverse takeover and had advanced our lead program into three clinical Phase 2 trials and one of our earlier programs into clinical Phase 1 development. We also established our corporate headquarters in New York, creating a truly transatlantic organization with a European subsidiary. It was a very productive and exciting year for us. An ever quicker and stronger transformation occurred with the COVID-19 pandemic when we recognized that our lead program, IMU-838, should clearly be tested as a potential treatment for SARS-CoV-2 infections, given its already known broad-spectrum antiviral activity.

We also expanded the leadership team and board. Several of us have worked together for many years as executive leaders at 4SC, which I co-founded in 1997. We already have a great and trustful working relationship and, last year, we rounded out the team with complementary experience and expertise that brings in fresh new thinking and even more dynamics.

Q: You've developed an advanced pipeline rather quickly. What can you tell us about it?

A: Immunic was founded when we bought two programs from 4SC, where three of Immunic's founders were part of the team that developed them. The discovery, preclinical development, and a bit of the early clinical work had been done, so we were able to get started very quickly. In fact, we dosed our first patient during the first week the company was open. Today, we have three assets in our pipeline:

– IMU-838 is an orally available small molecule investigational drug (vidofludimus calcium) that inhibits dihydroorotate dehydrogenase (DHODH) for which we recently announced excellent Phase 2 results for the treatment of relapsing-remitting multiple sclerosis (RRMS) and that is currently in Phase 2 testing to treat inflammatory bowel disease (IBD) with potential for other chronic inflammatory and autoimmune diseases. We recently initiated a Phase 2 trial in moderate COVID-19 disease based on IMU-838's previously known antiviral activity and positive in vitro data against SARS-CoV-2. IMU-838 is also being studied in an investigator-sponsored Phase 2 trial by the Mayo Clinic as a potential treatment for the rare disorder, primary sclerosing cholangitis (PSC).

– IMU-935 is a highly potent oral IL-17 inhibitor and selective inverse agonist of the transcription factor RORγt (retinoic acid receptor-related orphan nuclear receptor gamma) with additional activity on DHODH. Based on preclinical data, Immunic believes that it has potential as a best-in-class therapy for various inflammatory and autoimmune diseases. IMU-935 is currently in Phase 1 testing with plans to extend these studies in 2020 to assess safety and mechanism-related biomarkers in patients with psoriasis.

– IMU-856 is an orally available small molecule modulator that targets a transcriptional regulator of intestinal barrier function that we licensed from Daiichi Sankyo. Immunic believes it is highly innovative and potentially disruptive, representing a new treatment approach with a mechanism of action that targets the restoration of the intestinal barrier function in patients suffering from diseases like IBD or IBS-D and other intestinal barrier function-associated diseases. The Company expects that because IMU-856 avoids suppression of immune function, IMU-856 should maintain immune surveillance for patients. IMU-856 currently is in Phase 1 development.

Q: Can you discuss the challenges in developing new therapies for autoimmune disease?

A: I believe autoimmune disorders are very underserved, particularly when you consider the unmet need relative to the amount of research taking place. Especially in autoimmune diseases, I believe it's vitally important to truly hear what patients and their care providers have to say about what meaningful progress would look like to them.

In considering patient need, we took a very deep look at the benefits and shortfalls of existing treatments, and then thought about how we might substantially change the treatment paradigm. For MS patients for example, it might be something that prevents physical disability. By assimilating their perspective, everything takes on another color. It's what gets us up every morning with a sense of urgency to get to work and excited to make a difference.

Second, we found that one of the most important factors to keeping on track is to properly anticipate clinical trial recruitment potential. Of course, that's easier said than done.

For example, in one of our indications, we are competing for the same patients that other companies are also trying to recruit. In an ironic development, we had strong activity signals at a dose lower than anticipated, so we find ourselves enrolling patients for an additional cohort that we thought would end, so in a competitive environment, that impacts our timelines – but this is a good problem to have. A different trial enrollment was completed twice as fast as we expected based in large part on a smart trial plan, which made it attractive to patients and treating physicians.

So, it's important to carefully review the competitive trial landscape to predict speed of enrollment, but there will also always be some factors that are beyond your control.

Q: Do you see advantages of small molecules for autoimmune diseases?

A: The truth is that patients need both small molecules and biologics because they offer different benefits. Injectables have some obvious disadvantages to a simple daily pill, as well as a more complex supply chain and higher costs. That said, antibodies can have a benefit when it comes to specificity.

We have a lot of PK/PD data on IMU-838 as a result of the extensive work done prior to Immunic, and among the encouraging aspects we see are an excellent 30-hour half-life, a quick wash-out period, very good safety at the doses tested and no kinase inhibition, all of which lead us to believe there is potential for IMU-838 to be the first really safe and well-tolerated and easy-to-use treatment option for early RRMS. This may also allow for combination therapy with biologics. In addition, we recently obtained very strong Phase 2 data of IMU-838 in RRMS, underlining our belief that IMU-838 could provide RRMS patients with a distinctive combination of robust efficacy combined with favorable safety and tolerability.

Q: What is your business model as you approach late stage development?

A: We believe deeply in our assets and are committed to seeing them come to market. Therefore, we listed on Nasdaq in order to raise enough capital to see us through the next major value inflection points and to advance the assets by ourselves, if we so choose.

That said, if the right partner with the right deal comes along, we're open to it. In the future, we might make some decisions in this regard that create options for us, such as an ability to expand potential indications or advance another asset by making a deal.

Ultimately, we're very much open to deals with partners that we trust, that have the same commitment to the space and to the belief in high quality that we hold, and that offer a deal that makes sense for our mission and for our shareholders.

Q: What do you see as the advantages of maintaining a dual presence in both Germany and the US?

A: We've structured the company such that we've retained the strong research team's local ties to academia and industry in Germany, as well as connections to European regulatory agencies. At the same time, we have quick access to financial markets in New York and regulatory agencies in the US, all of which will be central to our long-term success.

Q: You recently exercised your option from Daiichi Sankyo on IMU-856. Why are you particularly excited about this compound?

A: IMU-856 reflects an entirely new approach for the treatment of gastrointestinal diseases, such as IBD or IBS-D, which is to restore intestinal barrier function by regulating genes linked with intestinal cell interactions and adhesion. It looks like it could have the ability to do so without impairing general immune function, which would be a kind of revolutionary new treatment for patients in this space. If successful, this approach potentially opens up whole new avenues for treating diseases of the digestive track.

Moreover, I'm also enthusiastic about this partnership. We developed a strong relationship with the team at Daiichi Sankyo over a period of time that actually predates this program. This long-term relationship has instilled a lot of confidence on both sides. As a result, we have complete belief in the quality of the data, and therefore in the program that we've taken over. We exercised our option to the exclusive global license in January of this year and while it's a bit of a risk, it underscores our enthusiasm and confidence.

Q: What are the near-term milestones on tap for Immunic in 2020?

A: 2020 is a very big year for us. I'll start with our lead asset, IMU-838. As mentioned, we initiated a Phase 2 trial in moderate COVID-19 disease. We already knew that the compound possessed broad antiviral potential, so we quickly assessed it in vitro against SARS-CoV-2 and determined that it showed enough activity to proceed quickly into clinical testing. Fortunately, IMU-838 has an attractive pharmacokinetic, safety, and tolerability profile and, to date, has already been tested in about 650 individuals, which should enable us to shorten the development timeline. In light of the global health crisis caused by COVID-19, we view this strategic expansion of our therapeutic focus as urgent and necessary.

Additionally, we announced strongly positive Phase 2 data in RRMS in August, reporting achievement of both primary and key secondary endpoints with high statistical significance. As such, we are prepared to start our Phase 3 program, which we're already actively planning now.

We expect to see data from our partners at Mayo Clinic in PSC in the first half of next year as well. Because there are currently no treatments approved for this condition, this program has the potential to advance quickly towards approval.

With regard to IMU-856, we initiated a Phase 1 trial in August 2020. As I mentioned, there is a lot of excitement around this molecule, both internally and externally in the gastrointestinal community, so we are looking forward to seeing this program advance.

Finally, we also reported initial Phase 1 safety and PK data from IMU-935 in healthy volunteers and initiated the expansion of the Phase 1 studies. In addition, we are currently in the process of identifying suitable orphan indications with high unmet medical need for further development of IMU-935.

While 2019 was an incredibly productive year for Immunic, 2020 is proving to be equally so. We've set a lot of goals for ourselves and I'm pleased that, to-date, we have established a record of executing on our plans and delivering what we've set out to. ◆

DEVICE DEVELOPMENT

Designing Devices for Inhaled Drugs

By: Andreas Meliniotis

INTRODUCTION

Not all medicines are suitable for delivery via a tablet or capsule, or even by injection or infusion. Some are best delivered via inhalation, often because they are treating a condition that affects the lungs, but with this route of delivery comes the requirement for a suitable device. Traditional inhalers and nebulizers can be difficult to operate, and require the patient to time their inspiration breaths with the drug's release. Additionally, devices may not be appropriate for all patients, such as pediatrics, or may also be difficult to operate for those with dexterity issues, such as osteoarthritis.

There is, therefore, plenty of opportunity for the development of new, improved devices to ensure inhaled drugs can be accessible for a wide range of patients and can treat various diseases and conditions effectively. The starting point when designing a new device should always be to define its target market, user needs, and possible regulatory pathway. Innovators need to work with engineers and designers to focus on who the device is for, and what the requirements of both the drug and the patient population are to ensure success.

With this list of top-level criteria in hand, the design process can begin. Usually, as an initial step, there would be a number of different concepts that are proposed, which are then ranked in terms of both benefits and disadvantages. Those that are the closest match to the requirements would be advanced through to the more detailed design stage, where practical considerations such as the devices' manufacturability and scalability would be assessed.

The next step is to take these detailed design concepts, and make sample devices using 3D printing or another rapid prototyping method. However good and detailed a drawing might be, it is not a substitute for a physical prototype, which allows a thorough assessment and gives a real sense of how it might work in the hands of a patient. Having a plastic device also allows tests to be carried out at an early stage as a dry run to reduce time later.

These prototype devices will also allow laboratory tests to determine how the formulated drug is likely to behave in the device and early mechanical tests to be carried out against those key functional parameters that were defined at the outset. These assessments will allow a list of critical quality attributes (CQAs) for the device to be defined.

INTO PLASTIC

If, after these initial studies, the proposed device looks to be promising, then a more robust prototype will be made. The use of computer-aided design and rapid

FIGURE 1

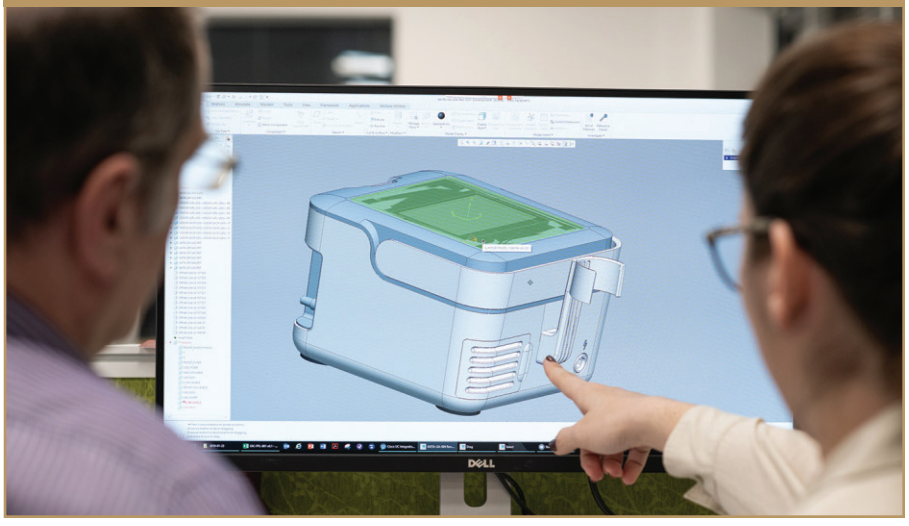


FIGURE 2

mould tools allow this to typically be completed within 6 weeks.

Rapid development tooling is an early investment that can pay substantial dividends later on. Prototypes made via 3D printing are adequate for early studies and assessment, but once multiple examples are required for testing in the laboratory, this becomes unfeasible. There are essential developmental tests that can only be done on rigid plastic prototypes, including drop tests and mechanical abuse level loading type tests, as well as environmental tests (the conditions of which are noted in ISO20072) that cannot be carried out effectively without a plastic device.

These prototypes will also be suitable for more functional tests, and tested against the functional specifications based on user needs. The user needs are independent of the product concept, whereas the functional specifications are testable and can be concept-specific. Table 1 shows examples of how functional specifications relate to user needs.

If the prototype meets all the requirements at this stage, the next step is device verification, again comparing it to the functional specifications. This will allow a traceability matrix to be created that will collate the evidence that it meets the functional specification and the list of user needs.

Human factors studies are particularly important in the design, as they look at how the device behaves in the hands of the likely user population. Initially, the studies will be conducted with relatively small numbers of subjects, and with the user groups that are most likely to show user errors. These may include the elderly, where common chronic conditions may mean there may be dexterity issues, or young children, who may not have the strength or coordination to operate the device effectively.

It is often easier to recruit healthy volunteers as subjects (or volunteers who are healthy aside from those dexterity issues). Such studies are an excellent tool for sifting out potential problems early on in the development process: in the long run, it will always be faster and cheaper to iron these issues out at an early stage than to progress a project into late-stage clinical trials only to have it fail because the device was not suitable. Rather, the best strategy is likely to be to create multiple iterations of prototypes, repeating the human factors studies each time, until a device that meets all the requirements has been identified. The amount of studies needed depends on the complexity of the user interface; typically five or six formative studies spaced across the device development cycle are required for a new device design, and a final validation study is conducted to demonstrate acceptable performance against the user needs, with a sample of the intended user population.

In terms of device design, a careful exploration of all the possibilities will assist in choosing the right concept from the outset and, if necessary, to head down a parallel path instead to ensure they are fully explored before committing to a specific design. Evaluating the human factors is essential in risk reduction and can be done in a comparative fashion when multiple designs, or elements of designs, are still being considered, thus guiding the design at relevant points in development.

The device development process typically follows a stage-gate process in which the project is reviewed with a board of representatives from across the relevant disciplines. The development is structured so that initially, the Target Product Profile (TPP), user requirements, including the user needs and intended uses, are reviewed at the first stage-gate, followed by the con-

TABLE 1

User Needs	Functional Specifications
The device shall be operable by the patient population	The device shall require no more than 10 N of force to operate the button
The device shall be portable	The device shall weigh less than 500 g
The device shall protect the drug from moisture	The doses shall be contained within individually sealed aluminum blisters

"The device development process typically follows a stage-gate process in which the project is reviewed with a board of representatives from across the relevant disciplines. The development is structured so that initially, the Target Product Profile (TPP), user requirements, including the user needs and intended uses, are reviewed at the first stage-gate, followed by the concepts at the second stage-gate, formal designs, device verification, manufacturing equipment, validation, and finally preparation for market."

cepts at the second stage-gate, formal designs, device verification, manufacturing equipment, validation, and finally preparation for market. The device performance continues to be monitored by post-market surveillance to assess whether lifecycle management activities are required. The reviews are conducted with representatives from a number of different disciplines to ensure every relevant aspect is reviewed prior to continuation through the phases.

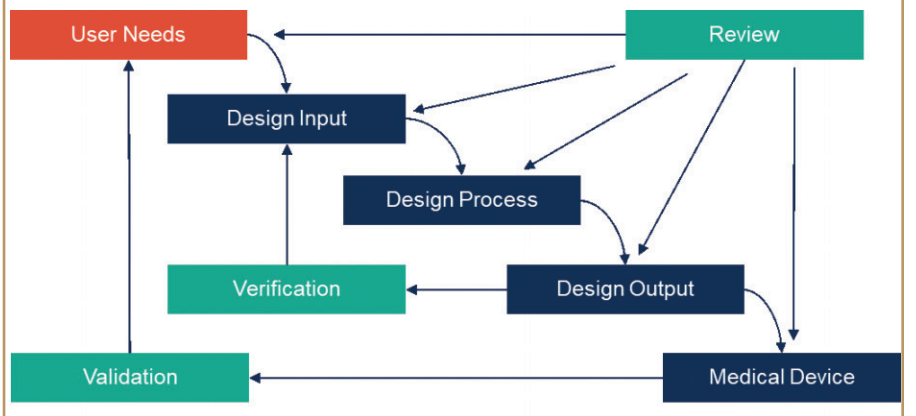
REGULATORY COMPLIANCE

It goes without saying that it is essential to align the device development process with the requirements of the regulators, and ensure that sufficient evidence of suitability is included in the registration package. Aligning with the waterfall diagram (Figure 3) in the FDA's 21 CFR Part 820.30 is a good place to start. The different regulatory bodies all have slightly different requirements, and it is important to include an assessment of whether it will meet the demands of the regulators in all the regions where the device is likely to be launched.

Defining the regulatory standards is another important process. Typically, in the design process, a list of 20 or 30 standards will be devised for each device development opportunity, and making sure the design aligns with this list throughout the process is crucial to succeed. Compliance with these standards should be carefully documented, otherwise there is a risk that at the end of the process, the result will be something that fails to meet them, wasting the time and cost of the project.

Correspondence with the regulators is another important consideration, as gaining regulatory input at an early stage increases the likelihood the device concept will be deemed acceptable. This type of interaction is also important when designing human factors validation studies to ensure the protocol is acceptable, and will therefore provide the required evidence that the design meets its intended uses. This correspondence can typically be conducted via a controlled correspondence route, which can also involve sending physical prototypes or require a physical meeting to demonstrate the device.

FIGURE 3



Source: Schematic from 21 CFR 820.30 FDA Design Controls Guidance for Medical Device Manufacturers (March 11,1997)

REDUCING RISK

In an ideal scenario, a new product will take advantage of an existing delivery platform as this affords a degree of proof that the product will be scalable to a commercial process, and issues around scale-up are less likely. Using laboratory-scale manufacturing to explore the design space of the product ahead of large-scale production can help ensure efficient costs and timescales. It will also assist the product getting into the clinic at a relatively early stage without having to invest in the expensive equipment and facilities required for a commercial product in place in advance.

There are multiple options for the delivery device and platform, and having experience from previous device development projects affords developers or CDMO partners a wider toolkit with which to work. Technologies, such as blisters, piercing, and winding up of blister strips, can be transferred readily across to new products once the knowledge as to how to assemble them and how they behave is known. This allows elements to be used with a different user interface, or another target market, and using those same general principles, experience and validated test methods from another device, greatly reduces the risk and time of development.

Applying statistical analysis to the test data allows the prediction of any likely problems once devices are being manufactured and filled at a commercial stage. If any issues are foreseeable, then this analysis will allow measures to be put in place in advance to reduce the potential of large numbers of returns, and the associated cost, accompanying poor publicity, and a loss of reputation.

Various different methods can be applied to reduce the risk. Paper-based exercises, such as tolerance analysis, can be used to assess the risk, while processes, such as failure mode and effects analysis, can also help, whether from the manufacturing, design, or human factors perspective. Using these outputs to guide development allows risks to be navigated and reduced as a project moves from an idea to a product that is ready for clinical trials and subsequent commercialization.

VALIDATION: A NECESSARY STEP

Verifying a product against a concept-specific and testable specification is one thing; from this one might expect to generate clear values that can be subjected to statistical analysis. Validation, however, requires going all the way back to the original list of user needs and proving that the device meets all those original requirements, not just the specifications that these were used to establish.

A good example of validation would be to carry out a human factors test in which the prototype is put into the hands of the patients. Importantly, they should be left to use it according to the instructions in the patient instruction leaflet. A clinical trial may also constitute validation that it does what it should.

Ultimately, it is important to remember the person for whom the device is being created: the patient. A device clearly needs to be robust, and deliver the product. But a design that is not patient-centric is unlikely to succeed. ◆

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHY

Andreas Meliniotis is Director of Device Development at Vectura, and leads the engineering and device development group based in Cambridge, UK. With over 15 years of experience at Vectura, he has led the design and development of several multi-dose dry powder inhalers as well as nebulizers and connected device technology. Prior to joining Vectura, he worked for the Cambridge Design Partnership and The Technology Partnership, developing glucose measurement devices and industrial printing technology respectively. He is a Chartered Mechanical Engineer and Chartered Manager, and earned his Bachelor's degree in Mechanical Engineering from the University of Nottingham, UK.

OVER-ENCAPSULATION CAPSULES

Double-Blind, Zero Bias: Over-Encapsulation — The Right Tool for Blinding Studies?

By: Julien Lamps

INTRODUCTION

Double-blinding is the key to pharmaceutical trial robustness and study integrity. While many blinding options are available to drug sponsors and external clinical research partners, over-encapsulation remains a popular choice for its dosing simplicity, trial efficacy, patient accessibility, and cost-effectiveness.

With marketing approval costs for a new drug exceeding $2.55 billion according to Tufts, the need to prove superior efficacy and safety is even more intense compared to an already approved and marketed product.[1] Beyond formulation and form, the method for visually blinding trial doses becomes a critical factor in determining efficacy and therapeutic performance. A properly blinded study removes both investigator and patient bias due to awareness of the drug's source and to suppress potential placebo effects as well.[2]

ENCAPSULATION INNOVATION

Today's patient-centric applications are demanding more from capsules than ever before. Fortunately, capsule technology is innovating to keep pace.

The DBcaps® line of capsules, for example, is specifically engineered for over-encapsulation in double-blinded clinical trial applications. Opaque with an extended cap length and dual locking rings, the tamper-evident design helps accomplish blinding's two primary functional tasks:

- hide the identity of the trial dose
- prevent people breaking open the capsule to see if they are being treated with a real drug or a placebo

In answer to pharma's need for innovation and a vegan, clean-label solution, Lonza Capsules and Health Ingredients (CHI) broadened its DBcaps® portfolio to include a Hydroxy Propyl Methyl Cellulose (HPMC) version in addition to the standard gelatin type.

KEY TO ENCAPSULATING SUCCESS

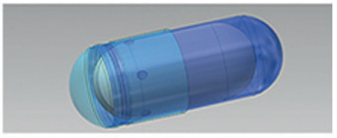
Though simple in practical terms, over encapsulating pharmaceuticals and blinding them for study involve several unique

FIGURE 1

Design is key

DBcaps® capsule design

Unique design of cap on body in closed position ensures more opacity



Standard capsule design

Risk for "breaking the blind" linked to single layer

"The key to successful over-encapsulation is to remember to treat each element of the process with the respect it deserves. From sizing and color to dose security and filling, each requires proper analysis and careful execution. This includes access to an experienced supply team dedicated to the capsule manufacturing process."

processes that can introduce complexities that may be tough to manage without support.

For example, blinding dose can become complex depending on the dose form. Encapsulating a split or broken tablet is a typical requirement. Similarly, different doses may be combined into the same capsule to meet specified requirements.

The key to successful over-encapsulation is to remember to treat each element of the process with the respect it deserves. From sizing and color to dose security and filling, each requires proper analysis and careful execution. This includes access to an experienced supply team dedicated to the capsule manufacturing process.

When each element of encapsulation is considered and managed carefully, fewer issues with this critical portion of the study are likely to occur at the end of the clinical trial supply chain, such as problems with formulation compatibility, bioavailability, and patient dose compliance.

PRIMARY CONSIDERATIONS FOR OVER-ENCAPSULATION

For clinical conditions in which the bioavailability of the investigational new drug is critical for efficacy, both the investigational and the reference drug should be encapsulated with the same capsule so that appropriate comparisons and conclusions can be drawn. It is important to select the appropriate components that will be needed to support the over-encapsulation of the tablet or capsule unit.

This is essential if one wants to obtain similar in-vitro dissolution profiles. Even when similar overall bioequivalence data (C_{max}, AUC) are achieved between non-encapsulated and over-encapsulated tablets, results may not necessarily reflect the drug absorption during the interval after dosing.

SIZE MATTERS

Once the trial dose form has been identified, determining what size capsule shell is needed to properly blind each unit comes next. But there are nuances to this.

For example, Lonza CHI has found through experience that efficiencies can arise if the dose being encapsulated does not protrude above the body of the over-encapsulating shell.

If the final dose does not "sit" properly inside the encapsulating shell, backfilling may be required to seat the final dose optimally. When this is required, it may become necessary to over-backfill the capsule, which can raise costs and waste.

FLEXIBILITY REQUIRED

A study design might call for splitting tablets to fit them into the smaller capsule sizes to suit patient group requirements. But splitting doses by breaking tablets physically is not precise and may introduce significant variation. Regulators addressed this by prompting drug developers to address these issues by filling capsules intended to study tablet OSDs with the formulation provided in powdered form to ensure dose accuracy. However, using an equivalent powdered formulation and filling it into capsules prior to blinding can add to program complexity and the demand for more flexible over-encapsulation solutions to fit more dose forms.

Capsule size is an extremely important detail to ensure trial supply dose compliance and blinding performance. To correctly specify the capsule size, one requires data and input from all corners of drug development, trial design, and administration as well as from critical supply, equipment, and fill-finish partners.

COLOR BLIND BY DESIGN

First and foremost, the color must completely hide the enclosed dose form. Ideally, the color and density of the capsule will absolutely blind any "details" of the

FIGURE 2

Capsugel® DBcaps® Capsules

contents. Anything that signals there is a trial dose inside could impact patient performance. Therefore, capsules for over-encapsulation are generally opaque and usually not the same color or shade of the dose being blinded.

It is vital to select a capsule color to effectively blind the enclosed dose, but it is also important that the color ingredients are accepted by regulators and meet standards wherever the study is being conducted.

Several countries have restrictions on particular colors or the total number of capsules. Compliance issues, including the foregoing, must be researched and understood prior to selecting trial sample colors.

MOTION CONTROL FOR BETTER BLIND CONTROL

Over-encapsulation ensures blind integrity because it completely hides the fact that the control dose is inside. This includes using a backfill excipient so that the trial dose cannot rattle around inside exposing the fact the capsule contains more than just powder or pellets.

If the rattle is not eliminated, the patient can possibly break the blind. Backfill can be avoided in certain cases, but only if a similar rattle between the doses can be maintained.

Lastly, when selecting backfill excipients, it may be convenient to choose one that is present in the dose form being blinded.

DON'T FORGET DISSOLUTION AND STABILITY

Probably one of the more critical issues with over-encapsulation selection is its general compatibility with the trial dose, the control dose, and any excipients. Consider the insolubility issues associated with today's highly potent APIs. Evaluating these factors is more important than ever.

The most commonly used excipients for backfilling are microcrystalline cellulose and lactose monohydrate, used both independently of one another as well as combined in a blend. Research has shown that the combinations of the two can influence dissolution results.

Depending on the grade of the material chosen, a lubricant, usually magnesium stearate (present usually less than 0.5%), is added as part of the backfill formulation. However, not all grades of these two materials require lubrication, and adding the magnesium stearate is usually based on its presence in the formulation of the unit being encapsulated in the first place.

It's imperative to conduct dissolution profiles and stability work early to verify that the material selected does not interfere with or create any bioavailability issues in the over-encapsulated dosage form.

STORAGE & SHELF-LIFE

Trial dose supply fill and finishers, among others, must also consider shelf-life and similar concerns with encapsulating shells — for some, storage and inventory control are extremely important issues.

Generally, if capsules are stored for more than 2 years, it is good practice to keep fresh supplies. Extended periods of storage in dry conditions can turn capsules brittle and make them prone to manufacturing issues related to the capsule's degraded physical properties.

Close consultation with suppliers may reveal better-performing gelatin capsule materials or alternatives that deliver both good performance and meet the industry's increasing quest for cleaner-label ingredients.

MORE OPTIONS, LESS CONFLICTS: GELATIN & HPMC

Developers of therapeutics of all kinds are responding to emerging social and cultural trends. These include increasing consumer demand for products free from any animal proteins and with colors and ingredients derived solely from natural sources.

Gelatin-based capsules offer traditional cost and functional benefits and remain the gold standard for pharmaceuticals and therapeutics of all kinds. The benefits supported by data to prove compatibility across thousands of applications.

However, emerging clean-label requirements are now starting to dictate that products should be free from animal proteins or colourings derived from artificial sources.

With potent NMEs under development, challenges deploying APIs in gela-

tin-based capsules are also contributing to a shift toward the use of HPMC-based capsules. Issues with cross-linking reactions and difficulty containing hygroscopic APIs top the list of these challenges.

For a broad segment of drug delivery strategy, HPMC-based capsules show great potential in becoming the best-practice alternative to gelatin-based formulations, not only because of their provenance, but also for their performance.

SUMMARY

Over-encapsulation remains a widely used, highly effective technique for blinding solid oral dosages in comparative clinical trials. Compatibility is foremost. Dissolution, diffusion, and stability studies are essential elements of selection and therapeutic performance. In addition, patient-centricity is shaping the selection of materials and specifying criteria, leading to the introduction of innovative clean-label products like HPMC-based capsules compatible with vegetarian and vegan lifestyles.

Although HPMC-capsules offer a range of development benefits, traditional hard-gelatin capsules are still the first choice for blinding studies. However, more viable choices are available now than ever before, which increase sponsor flexibility and give them greater freedom in patient trials and fewer compromises regarding product compatibility and format.◆

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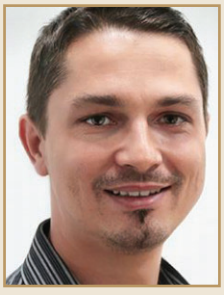

Julien Lamps is Product Manager at Lonza Capsules and Health Ingredients. He graduated from Ecole Nationale Supérieure de Chimie de Lille with an Engineering degree in Chemistry in 2004. He joined Capsugel as a Quality Assurance Engineer in the Colmar plant in 2011, and in this role, he worked at the interphase of operations and customers within the well-known Capsugel® Quality Mindset. During this time, he specialized in coordinating new product introductions to develop innovative offers around modified-release profiles and inhalation products.

Drug Development
EXECUTIVE

Rajiv Khosla, PhD
CEO
Enteris BioPharma

Enteris BioPharma: Pioneers in Oral Formulation Development

Breaking down the barriers to oral delivery of peptides and small molecules is no easy task, but it holds the key to enhancing myriad drug products and treatment paradigms. Presently, many of these therapies can only be administered parenterally due to poor oral bioavailability or permeability, which can limit market opportunities for the drug maker and reduce patient compliance with treatment regimens. Enteris BioPharma, an emerging biotechnology company based in Boonton, NJ, offers a solution to these challenges.

Founded in 2013, Enteris has established itself as a pioneer in the oral peptide market, utilizing its proprietary drug delivery technology, Peptelligence®, and its manufacturing capabilities to develop and produce oral formulations of BCS class III and IV compounds, including peptides, peptidomimetics, and small molecules. Through Enteris' own internal R&D program and external partnerships, Peptelligence is now the subject of several pre-clinical and clinical development programs. *Drug Development & Delivery* recently interviewed Dr. Rajiv Khosla, Chief Executive Officer of Enteris BioPharma, to discuss how Enteris' innovative oral formulation technology is helping the pharmaceutical industry overcome the hurdle of low bioavailability to reshape treatment categories and expand market opportunities with minimal financial and regulatory risks.

Q: Dr. Khosla, you were appointed CEO of Enteris BioPharma in May. What drew you to the company?

A: From its founding in 2013, Enteris has established itself as a leader in the oral peptide market, yet I believe the company has only begun to realize its vast potential. The Peptelligence oral delivery technology is a potential game changer for pharmaceutical companies that offer the opportunity to not only enhance myriad drug candidates, but also reshape therapeutic categories and treatment paradigms in ways that can fill unmet medical needs and provide improved treatment options for patients. For the CEO of a specialty drug delivery company, that is quite an opportunity.

This is a growing company with a number of value-creating opportunities on the horizon. The acquisition of Enteris last year by SWK Holdings (Nasdaq: SWKH) provided a strong validation for Peptelligence and the company's future prospects. With SWK's commitment, Enteris now has a partner who shares our excitement for the technology's potential and is willing to invest capital and other resources to advance the company's internal and external development pipelines, bolster our management team, strengthen our business development activities, and fund a major expansion of our manufacturing capabilities.

Q: Enteris' Peptelligence platform is designed to enable the oral delivery of peptides, peptidomimetics, and other BCS class III and IV molecules. Can you explain the significance of this capability and Enteris' approach?

A: The oral delivery of peptides, peptidomimetics, and other BCS class III and IV molecules are often hampered by low bioavailability and permeability. As such, these drugs are typically administered by injection, which limits market penetration and patient compliance. Oral formulations, however, can improve patient adherence to drug regimens. Afterall, who would not choose to swallow a tablet rather than endure a painful injection. For drug makers, it can expand the market for newly discovered molecules and is an excellent lifecycle management strategy for commercial products nearing the end of their life cycles.

There are other advantages. Perhaps one of the most underappreciated is the reduced regulatory risk facing drug makers. The reformulation of an existing drug can open the door to the 505(b)(2) regulatory pathway through the U.S. FDA, which allows a drug maker to take advantage of existing safety data. This can reduce the financial cost of drug development and minimize the regulatory risk when compared to the costs and risks associated with the development of a new chemical entity (NCE).Yet, the value of the 505(b)(2) regulatory pathway, in my opinion, has not been fully explored by the broader biopharmaceutical industry.

Through our licensing agreements and partnerships with other drug makers, Peptelligence is now the subject of several active externally sponsored pre-clinical and clinical development programs. Among these programs is an oral formulation of Cara Therapeutics' KORSUVA™, a potent peripheral kappa opioid receptor agonist with a primary focus for the treatment of pruritus associated with kidney failure, liver disease, and atopic dermatitis. Cara is currently advancing three oral KORSUVA clinical programs for these three distinct treatment indications. Enteris is also harnessing Peptelligence to develop its own internal clinical pipeline of orally delivered therapeutics that have been previously marketed as injectable-only formulations.

Q: The backbone of Enteris' business is partnering with companies to design and advance oral tablet formulations of the partner company's peptide or small molecule drug product. What sets Enteris apart from its rivals? What makes you the preferred partner for pharmaceutical companies?

A: There are many factors that set Enteris apart from our competitors, but these encapsulate what I believe are of greatest value to our current partners and prospective future partners: the strength of our technology and what it can accomplish, strong intellectual property protection, a collaborative approach with a focus on customization and our manufacturing expertise.

The Peptelligence oral formulation technology utilizes several patented oral bioavailability-enhancement techniques, using a variety of conventional pharmaceutical formulation methods and pharmaceutical excipients. We do not offer a single off-the-shelf technology but work with our partners to develop formulations that are specifically bespoke and optimized for their active pharmaceutical ingredient (API). We closely examine the characteristics of the API, the potential indications, the status of the development program, and the feasibility of oral delivery. It is typical for Enteris to provide three or more formulation prototypes to partners to demonstrate the feasibility of the Peptelligence oral formulation technology.

Peptelligence enhances bioavailability by solubilizing and improving the permeability of APIs across a wide range of

molecular weights. The result: Peptelligence enables the oral bioavailability of APIs that previously had zero oral absorption or enhances by up to 11-fold APIs with poor bioavailability. Moreover, Peptelligence has been validated in more than 15 clinical trials and benefits from robust clinical and safety experience.

The Peptelligence pharmaceutical manufacturing process is a highly scalable and straight forward procedure that uses methods, such as dry blend and direct compression, to produce dosage forms that readily satisfy in-process controls and release testing. And finally, our partners benefit from robust intellectual property protection in the U.S. and internationally in key markets through 2036.

Q: Adding to Enteris' strength as a development partner is the company's manufacturing capabilities. What manufacturing expertise do you bring to the table that differentiates Enteris? Why is the expansion of Enteris' manufacturing capabilities important to the company's growth?

A: The formulation, development, and manufacturing of oral, peptide-based drugs is a complex business and requires specific skills and expertise. Enteris is uniquely positioned with the capabilities and expertise to meet an array of manufacturing needs within this niche. We are especially proud of our established track record spanning over 23 years with a history of quality focus and regulatory compliance.

We are experts in handling and processing high-potency APIs. We have experience working with biopharmaceutical companies of all sizes. Our CDMO operations are housed in a growing 32,000-sq-ft facility in Boonton, NJ, with the capability to scale-up and cGMP manufacture optimized oral formulations to meet clinical trial needs from feasibility to Phase 2, and provide analytical development and stability testing, with a proven enteric-coated tablet formulation that is scalable and readily transferable.

An expansion project has been underway at our manufacturing facility. Completion is expected in the short-term and will enable us to manufacture Phase 3 clinical trial material (CTM), and commercial-level production. This will allow us to pursue deeper manufacturing relationships with developmental clients and allow us to remain a trusted and reliable manufacturer as client programs progress through each stage of drug development.

Q: Enteris is also advancing its own internal pipeline of oral peptide and small molecule therapeutics. What is the company's strategy and what are your lead programs?

A: We believe that developing an internal pipeline that leverages the Peptelligence platform will enhance the value of the technology. Enteris has developed a strong regulatory strategy involving the use of the 505(b)(2) regulatory pathway. But our goal is not to become a commercial drug company, but rather to seek partnerships and out-licensing opportunities and use that capital to fund future growth.

Our most advanced clinical-stage drug candidate, Ovarest®, is a Phase 2b-ready oral formulation of the peptide leuprolide that we are developing for the treatment of orphan indications. It is followed by Tobrate™, an oral tablet formulation of tobramycin, now in Phase 1 development for the treatment of uncomplicated urinary tract infections (uUTIs).

These are attractive development opportunities. In the U.S., urinary tract infections affect approximately 10 million women annually. Leuprolide, on the other hand, is an effective and widely used therapy, but has significant limitations in both convenience and tolerability due to its depot injection delivery method.

Q: Looking ahead, what do you see as the key opportunities for Enteris over the next 6 to 12 months?

A: We entered 2020 with a great deal of momentum and continue to target multiple growth opportunities. To that end, we are excited about the ongoing expansion of our manufacturing facilities. Completion is expected in the short- term and will enable us to manufacture Phase 3 CTM and commercial-stage compounds.

Meanwhile, Enteris continues to pursue new external licensing and partnership opportunities for Peptelligence and advance its internal and partnered pipeline assets. ◆

- Integrated Data
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OSD FORMULATIONS

Dissolving Bioavailability & Solubility Challenges in Formulation & Development

By: Vinod Patil, PhD

INTRODUCTION

An increasing number of highly potent and complex small molecule formulations are entering development pipelines. A preferred dose form, oral solid dose (OSD) formulations, continue to lead drug research, development, and approvals - 2019 saw the highest percentage of OSD approvals since 2013.

According to the US FDA Center for Drug Evaluation and Research (CDER), of the 38 small molecule drugs approved by the agency in 2019, 26 (68%) were OSDs (19 tablets and 7 capsules). Notably, one New Molecular Entity (NME) was approved both for oral and parenteral delivery.

Many of the innovative and novel formulations introduced by the pharma industry throughout the past decade have had to cope with poorly water-soluble active pharmaceutical ingredients (APIs). Considering the pace of development, overcoming solubility issues will remain problematic. This is especially true for important new classes of pharmaceuticals entering the market.

Poorly water-soluble API chemistries require much more than a neutral excipient to deliver the dose. Overcoming bioavailability and solubility issues can bog down development and slow commercialization timelines because formulators often face a cascading set of complexities trying to deliver their API payloads with accuracy.

Facing down insolubility issues requires a comprehensive understanding of the physiological pharmacokinetic and pharmacodynamic processes that happen between swallowing the dose and its uptake *in vitro*.

RECENT NMES CONTINUE THE SOLUBILITY CHALLENGE

Innovation in combinatorial chemistry and other recent advances in pharmaceutical and biopharmaceutical science are leading to exciting new discoveries and patient breakthroughs. Although APIs in these drug products may ultimately offer extremely good therapeutic performance, if they cannot enter the bloodstream efficiently from an orally administered solid

FIGURE 1

Overcoming bioavailability and solubility issues can slow commercialization timelines because formulators often face a cascading set of complexities trying to deliver their API payloads with accuracy.

dose, overall drug strategy can be compromised.

It's extremely challenging because formulators face a broad range of compromises they might not want for their drug because of patient and standard- of-care terms – for example, not surrendering the formulation to parenteral delivery for the sake of patient convenience and dose compliance.

Enhancement of dissolution, solubility, and bioavailability for poorly soluble APIs can be achieved using a number of different approaches, including particle size reduction (eg, micronization and nanomilling), salt or cocrystal formation, lipid-based self-emulsification, and the formation of amorphous solids dispersions (ASDs).

Regardless, many new compounds and chemistries have either low solubility or low bioavailability or both. As such, they present unique challenges to formulators depending on their drug delivery strategies.

INCREASING SOLUBILITY

To assist therapeutic performance, there are generally two ways to increase solubility: 1) a chemical modification approach or 2) a formulation approach. Chemical modifications include either taking a pro-drug approach or employing a salt form of the drug. Most formulators understand there are increasing degrees of complexity involved in using a salt form to increase solubility due to the need to develop salt form synthesis and purification methods.

That's why formulation methods, such as micronization, amorphous solid dispersions, nanocrystals, and nanoparticularization techniques, are increasingly popular in the field of solubility enhancement.

FIGURE 2

To increase solubility of APIs, two common approaches - chemical modification or formulation are available. Chemical approaches have proven utility, but formulation methods, including micronization, amorphous solid dispersions, nanocrystals, and nanoparticularization, are becoming increasingly popular to support therapeutic performance.

MICRONIZATION'S TOP-DOWN APPROACH

Two principles are being used to produce nanoparticles: top-down approaches like milling or ultra-homogenization, and bottom-up approaches including precipitation. Micronization is a simple approach, in which the particle size of the API is reduced, leading to higher particle surface area and eventually better solubility performance. Although these concepts have shown positive results for many drugs, there are some APIs that need further formulation techniques to increase solubility.

NANOCRYSTALS EMERGING AS AN EFFECTIVE ROUTE

Nanocrystalization is an emerging technology that is helping formulators deal with the challenges of improving the solubility and bioavailability of their poorly soluble APIs. Nanocrystals will account for 60% of a $136-billion nanotechnology-enabled drug delivery market by 2021.[1]

Essentially, crystalline particles range in size from 2 nm to 1,000 nm. Nanocrystals are ground in special mills, and the procedure enhances the surface-to-volume ratio and thus, the solubility and bioavailability of most insoluble pharmaceuticals.

Due to crystalline characteristics, they offer better stability compared to their amorphous counterparts. In addition to bead milling, nanocrystals can be prepared by high-pressure homogenization and precipitation.

FIGURE 3

Target-specific and site-specific drug delivery is gaining momentum among pharma's developers. New technologies and techniques are being employed offering developers more options and fewer compromises.

MORE SURFACE AREA, FASTER DILUTION RATES

Nanocrystals work to improve solubility through an increase in surface area beyond that provided by just micronization. This is especially helpful in improving solubility of drugs in which it is limited by dissolution rate. Amorphous nanoparticles are even more advantageous in improving solubility, but they come with the challenge of requiring stability to prevent conversion to the crystalline forms.

Another characteristic of nanocrystals that supports therapeutic performance is the fact that particles are 100% API and require no excipients.

Due to crystalline characteristics, they offer better stability compared to their amorphous counterparts and can be administered as dispersions in the liquid medium or in the solid state.

Nanocrystals can also be prepared by bead milling, high-pressure homogenization, and precipitation. One of the main advantages of this technology is it allows for higher API drug loads per dose. However, this process requires surfactants as stabilizers, which may prompt new formulation complexities or other negative effects.

GETTING DRUGS OVER THE TARGET

Apart from these methods, target-specific and site-specific drug delivery is gaining renewed momentum among pharmaceutical developers. Nanoparticulate methods and technologies being employed now are well understood and offer developers broad utility and fewer compromises when it comes to managing optimal dose delivery.

For example, many developers are turning to enteric-coated multiparticulate systems in tablets and capsules. This technology is demonstrating great utility and functionality particularly for acid-sensitive drugs.

Nanoparticulate technology is transforming the industry's ability to successfully formulate poorly soluble APIs. Nanoparticulate formulations of poorly dissolving APIs can provide faster drug absorption and higher bioavailability by increasing dissolution rate.

When it comes to developing challenging compounds, it helps if the scientists know whether the client has performed preliminary solubility studies, any kind of simple animal PK studies, or even what the critical quality attributes are, such as modified release or the need to deliver the drug in the small intestine.

SOLVING AN ACID DEGRADATION PROBLEM

A Metrics client had an API susceptible to acid degradation and general hydrolysis, which meant it had to be protected from stomach acid. In addition, exposure time to fluid in the small intestine needed to be minimal.

Following analysis, it became apparent an enteric coating was needed to provide acid protection. As a second line of defense, chemists incorporated muco-adhesive polymers into the core tablet, to help it adhere to the walls of the small intestine.

This allowed the actives to permeate across the small intestine, where it then was hydrolyzed to the API. Despite the challenge of preventing hydrolysis throughout transit in the stomach and small intestine, animal studies confirmed that it provided bioavailability of the molecule of interest.

"Innovation in combinatorial chemistry and other recent advances in pharmaceutical and biopharmaceutical science are leading to exciting new discoveries and patient breakthroughs. Although APIs in these drug products may ultimately offer extremely good therapeutic performance, if they cannot enter the bloodstream efficiently from an orally administered solid dose, overall drug strategy can be compromised."

AMORPHOUS PARTICLE FORM DISPERSIONS

Many APIs available today are crystalline in nature and exhibit poor solubility. However, crystalline APIs can be converted into amorphous particle forms, shaped to offer more surface area. Generating ASDs is well understood and accomplished commercially using spray-drying technologies.

Preparing an API into an amorphous form rather than a crystalline state can support desired dissolution profiles and enhanced bioavailability. However, because amorphous compounds are thermodynamically less stable, it is often necessary to employ polymeric matrices to improve their stability.

Once ASDs reach the GI tract, the API is released in concentration. According to one study, more than 80% of amorphous dispersions offer improved dissolution rates and bioavailability.[2]

ORAL ADMINISTRATION, THE PATIENT-CENTRIC GOAL

Amorphous dispersions offer drug formulators the ability to deliver an OSD final drug product in the form of a tablet or a capsule. ASDs allow the formulation of drug products with much higher dosage levels compared to lipid-based systems. Ultimately, these formulations allow for more API in a single dose, and that means more medication in fewer doses for patients.

CASE STUDY: ONE-AND-DONE FORMULATIONS

A Metrics Contract Services client needed support for a commercialized drug product indicated for curative treatment. The intellectual property owner was hoping to develop a second-generation formulation for a clinical trial studying the drug's efficacy as a preventive treatment. The clinical trial expected to enroll patients for whom medication compliance was a primary issue and could impact dose compliance. Thus, the client hoped to encourage patient compliance with an easy manageable "one-and-done" daily dosing.

The developer's second-generation iteration required almost every deliverable a formulation development scientist could imagine — uniform-sized multi-particulate for consistent controlled release; taste-masking and a smaller particle size to improve patient compliance; not to mention a 24-hour modified release for once-a-day dosing; and dose dumping prevention.

A MULTI-FACETED APPROACH TO A CHALLENGING FORMULATION

This situation was a first for Metrics senior formulation scientists. Never had they encountered a project with so many formulation development deliverables. With most projects, Metrics commercial partners choose two or three deliverables that are most important. But this clinical trial would involve unique patients who could easily fail to carry out a medicine regimen, so compliance was critical and challenging.

The Metrics team established critical quality attributes that were achievable for the product — the most important attribute being controlled release for 12 to 24 hours. The API's highly water-soluble nature posed significant challenges to achieve any kind of controlled release.

Controlled release was achieved by layering the drug onto a substrate and then applying a completely insoluble functional coat using a solvent-based coating system. The downside of achieving the controlled release was the large amount of drug product needed to achieve a therapeutic dose concentration of 25% to 35% w/w.

However, Metrics was able to increase the drug concentration by making pellets of the drug through extrusion and

spheronization. The next steps for this complex dosage form were to increase patient compliance through taste-masking and making a suspension of the pellets.

THE OUTCOME

The team created a highly water-soluble compound in a dosage form with controlled release. Despite using a completely insoluble coating, the team was able to push API out from the center of the beads. The functional coat consisted of completely insoluble material (ethyl cellulose and dibutyl sebacate as the plasticizer) and yet drug product still released from the core. Metrics found that using a solvent system, as opposed to an aqueous dispersion and cure times, gave a nice, contiguous coat that could provide the desired controlled release.

The client used the formulation to successfully conduct a Phase 1 clinical trial. The company is proceeding to Phase 2 clinical trials leveraging the same formulation process Metrics developed using a different starting substrate.

DISSOLUTION TESTING'S MAJOR ROLE

Many pharmaceutical analysis tools are used to characterize a drug product, but dissolution testing plays an important role in defining the performance of a drug ensuring product quality.

There are many reasons why dissolution testing is so important. Dissolution testing is the only pharmaceutical tool that can assess both drug product performance and adherence to key quality attributes based on the design of the drug.

From simple immediate-release formulations to complex modified-release formulations, an accurately developed dissolution method is critical for confirming product quality over time and under various conditions.

If an *in-vitro* dissolution testing procedure shows significant correlation with in-vivo clinical data, it can provide predictive modeling that may eliminate the need for additional clinical studies over the product's lifetime. Not only can dissolution provide valuable predictive modeling, it can also help resolve unexpected bioavailability results.

Biorelevant dissolution media is ready to bridge the gap between a quality control procedure and predictive modeling as a measure of pharmacological clinical relevance. Dissolution testing also provides support for formulation development and prototype selection — either during early phase development or in support of post-approval changes.

While stability indication of an assay and the impurities procedure is scrutinized during Chemistry, Manufacturing, and Controls (CMC) review, dissolution data helps gain the focus to ensure the optimal procedure is developed.

Indeed, many regulatory guidance documents have been published requiring a gradual progression of dissolution throughout the phases of drug development or in support of Scale-Up and Post-Approval Changes (SUPAC) requirements.

LAST WORDS ON SOLUBILITY

For drug developers and their commercial drug product manufacturing partners, there is likely no "last word" regarding improving the solubility of today's prominent APIs. Although innovation is introducing new challenges, lifecycle management and new marketing strategies are also prompting developers to dissolve the solubility issues of existing products. Ultimately, the effort and investment will continue as pharma seeks to deliver improved products to patients.◆

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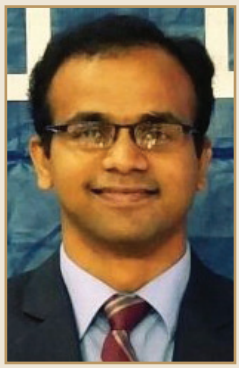
BIOGRAPHY



Dr. Vinod Patil is Manager, Pharmaceutical Development at Metrics Contract Services, directing a team of formulation scientists and specialists who develop novel oral solid-dose formulations for Phase 1 through Phase 3 clinical trials, and then scale-up and support of the validation and commercialization of those products. He provides technical leadership and oversees GMP compliance on a variety of ongoing formulation and process development projects. He assists in budget planning and works with client services on service estimate generation, assignment deadlines, and other matters related to new business development. Dr. Patil earned his BS in Chemical Engineering from the Institute of Chemical Technology in Mumbai, India and his PhD in Chemical Engineering from the University of Kentucky.

CUSTOM DEVICE SOLUTIONS

Device Design Will Act as Competitive Distinguisher in a Post-Patent Expiry Biosimilar Market

By: George I'ons

INTRODUCTION

The biosimilars landscape is rapidly evolving; we've seen a vast number of original reference biologics reach expiry for patent exclusivity – 15 in the US during the 2018-2023 period alone - and the market opportunity for biosimilar manufacturers expand in parallel.[1] As some of the world's best-known biologics continue to reach patent expiration, the approval and uptake of biosimilars is expected to pick up even more over the coming years. The US market is poised to welcome many new biosimilars in 2020, spurring competition that will inevitably lead to savings for the healthcare system. In fact, introducing biosimilars of complex biologic drugs used to treat illnesses such as rheumatoid arthritis could cut healthcare spending in the US by $54 billion throughout the next decade.[2] Yet, this market incentive may not suffice to really drive biosimilar uptake. For biosimilar manufacturers to succeed within this freshly competitive market, they will need to factor in several crucial non-price aspects into their product offering. The following will dissect the different factors that will determine biosimilars' adoption and pace of advancement against their original counterparts, namely clinical confidence in the biosimilar and patient confidence in the drug delivery device.

DEMONSTRATING INTERCHANGEABILITY

Switching patients from original biologics to biosimilars is not necessarily an easy or required procedure. While biosimilars are highly similar in structure, biological activity, and immunogenicity profile to their already approved biopharmaceutical reference product, their active ingredients are not identical to the original product, and the natural variability and complex manufacturing process of biosimilars do not allow for an exact replication.[3] This is undeniably a potential source of existing concerns about swapping from one product to another. Today, there is still not enough evidence to demonstrate a total interchangeability between the original reference biologics and their respective biosimilars, and regulators such as the FDA are demanding an increasing level of data to support biosimilar approval. While regulators in global markets may continue to act with due caution in designating biosimilars as interchangeable, some independent studies have started to fill in the gaps with evidence of such a transition being well-tolerated by patients and demonstrating equal efficacy and safety as

FIGURE 1

As some of the world's best-known biologics continue to reach patent expiration, the approval and uptake of biosimilars is expected to pick up even more over the coming years.

their originator medicine.[4] With these, confidence in biosimilars for their approved indications has grown and alleviated some of the initial concerns about their use, particularly when initiating therapy in patients.[5]

THE ROLE OF DRUG DELIVERY DEVICE DESIGN

Beyond the general confidence in biosimilars as an equally efficient and safe biologic alternative, cultivating physician and patient confidence in a specific biosimilar product and its drug delivery device is also crucial to biosimilar uptake. With self-administration among patients with chronic illnesses on the rise, the importance of the design of the subcutaneous injection device is more important than ever before and may become a deciding factor for patients who are eligible for a switch to a biosimilar. Given that the treatment of chronic illnesses may require frequent injections, and that patients are increasingly carrying these out themselves, patient usability and ease-of-use should be high on the list of considerations for biosimilar manufacturers when partnering with medical device manufacturers or particularly if designing their own injection device.

More specifically, devices with hollow-bore needles or syringes that retain an exposed needle after use present a heightened risk of needlestick injury, while auto-injector or prefilled safety syringes typically minimize this risk and minimize the risk of dosage errors.[6] Allowing older, debilitated, and less-dextrous patients to securely hold and operate the device without any assistance, these instruments contribute to providing patients with the independence that comes with self-administration, while reducing the risks associated with unsupervised self-care. Similarly, with patients who self-administer having to bring the delivery device into their homes, ensuring total safety for their families and other residents will be of utmost importance to them. Equally, safety syringes help protect hospital and non-hospital healthcare workers against potential infection through sharps. A safe, user-friendly device may be the tipping point that pushes existing users to accept a loss of habit and familiarity in the name of usability and confidence.

Under these circumstances, it is strategically necessary for manufacturers to carry-out human factors studies to support the design and development of their device in order to mitigate any potential risks associated with the use of the device, and seek to eradicate these risks with best-practice design. It will be crucial for biosimilars manufacturers seeking to encourage patient adherence to be able to demonstrate that user-associated risks have been thoroughly assessed and addressed – and doing so successfully will act as valuable competitive distinguisher within this highly competitive post-patent market. Some pharmaceutical manufacturers are even known to have made exclusive arrangements with device manufacturers as a means of ensuring a monopoly over an efficient device design and providing their biologic product with a competitive edge.[7]

FIGURE 2

Prefilled safety syringes reduce the risks associated with self-administration.

CONSIDERATIONS DURING THE DEVELOPMENT PROCESS

To delve further into the specific elements that should be factored into the design during device development, it is the interface with the primary container that will first require careful consideration. Throughout each stage of the development process, manufacturers will need to keep a careful eye on all things relating to regulatory compliance of the device, particularly in light of the growing complexity and scrutiny of regulatory requirements, as well as compliance with key relevant standards. As previously mentioned, human factors studies will be the next stage of the device design process, which will need to be undertaken in an all-encompassing manner, as well as factoring in ISO10993 compliance for biocompatibility of materials for cytotoxicity, irritation, and skin sensitiza-

tion. Commentators recommend paying special attention to the following list of considerations: usability and robustness; assembly and manufacturing risk management; supply chain reliability; environmental/disposal risks, and post-shipping device performance as part of the development process.[8] On a final note, keeping the design review process open and transparent by compiling a complete design history file will also be beneficial for device manufacturers in demonstrating effective risk-assessment and providing confidence to their pharmaceutical and biotechnological partners.

SUMMARY

Our own research has estimated the market opportunity for biosimilars to be $5.24 billion per year in the US – making this window of opportunity a lucrative one.[9] However, getting a slice of this cake means not perceiving biosimilar adoption as a given. Biosimilar manufacturers will need to demonstrate true interchangeability of their product with its original reference product, while also capitalizing on the competitive edge that comes with offering an attractive, user-friendly, and safe delivery device if they are to increase their market shares. When all user-related considerations have been addressed, manufacturers must also be sure to consider all other stages of the device production, from the primary container of the device to its packaging, to further set themselves apart from the competition. ◆

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BIOGRAPHY

George l'ons is currently Head of Product Strategy and Insights at Owen Mumford, having worked for the former OEM and now Pharmaceutical Services division of the organization since 2006. His current focus is on deciphering the rapidly changing pharmaceutical and biotech sectors in relation to their needs for combination products. In his previous roles in business development, he worked closely alongside R&D to develop devices for a variety of global pharmaceutical and diagnostic clients. Prior to Owen Mumford, he worked for Abbott in EMEA marketing roles in Germany, focusing on their diabetes business.

IMMUNOGENICITY TESTING

Regulatory Updates for Immunogenicity Assessment of Therapeutic Proteins

By: Leon Shi, PhD, Lan Li, MS, and Jing Shi, PhD

INTRODUCTION

Immunogenicity assessment is a significant challenge in the development of therapeutic proteins, such as monoclonal antibodies, recombinant proteins, antibody-drug conjugates, and fusion proteins. Due to high molecular weight, complex structure, and post-translational modifications, biologics have high potential to illicit anti-drug antibodies (ADA) responses. Developing adequate strategies for immunogenicity evaluation is therefore crucial for preclinical and clinical development of biologics programs. These ADAs — whether neutralizing antibodies (NAbs) that block efficacy of a protein by targeting domains critical for function or non-neutralizing antibodies — can have significant consequences, affecting a product's pharmacokinetics (PK), pharmacodynamics (PD), drug efficacy, and safety.[1]

In early 2019, the FDA updated its guidelines for immunogenicity testing and recommended a risk-based approach to evaluating and managing immune responses elicited by therapeutic proteins. Timing and extent of developing, validating, and implementing ADA assays during the drug development stage are dependent on the risk assessment of the product.

The following provides a high-level analysis of the significant changes to the guidance compared to the immunogenicity draft guidance released in 2016, and the implications for drug development programs.

WHAT'S DIFFERENT IN THE 2019 GUIDANCE?

The significant revisions focus on the following areas:

- Risk assessment and timing on validating assays
- Statistical approaches to determine cut-point
- Removal of the long-term stability requirement
- Development of assays to measure neutralizing antibodies
- Strategies for managing pre-existing antibodies
- Updates in documentation requirements.

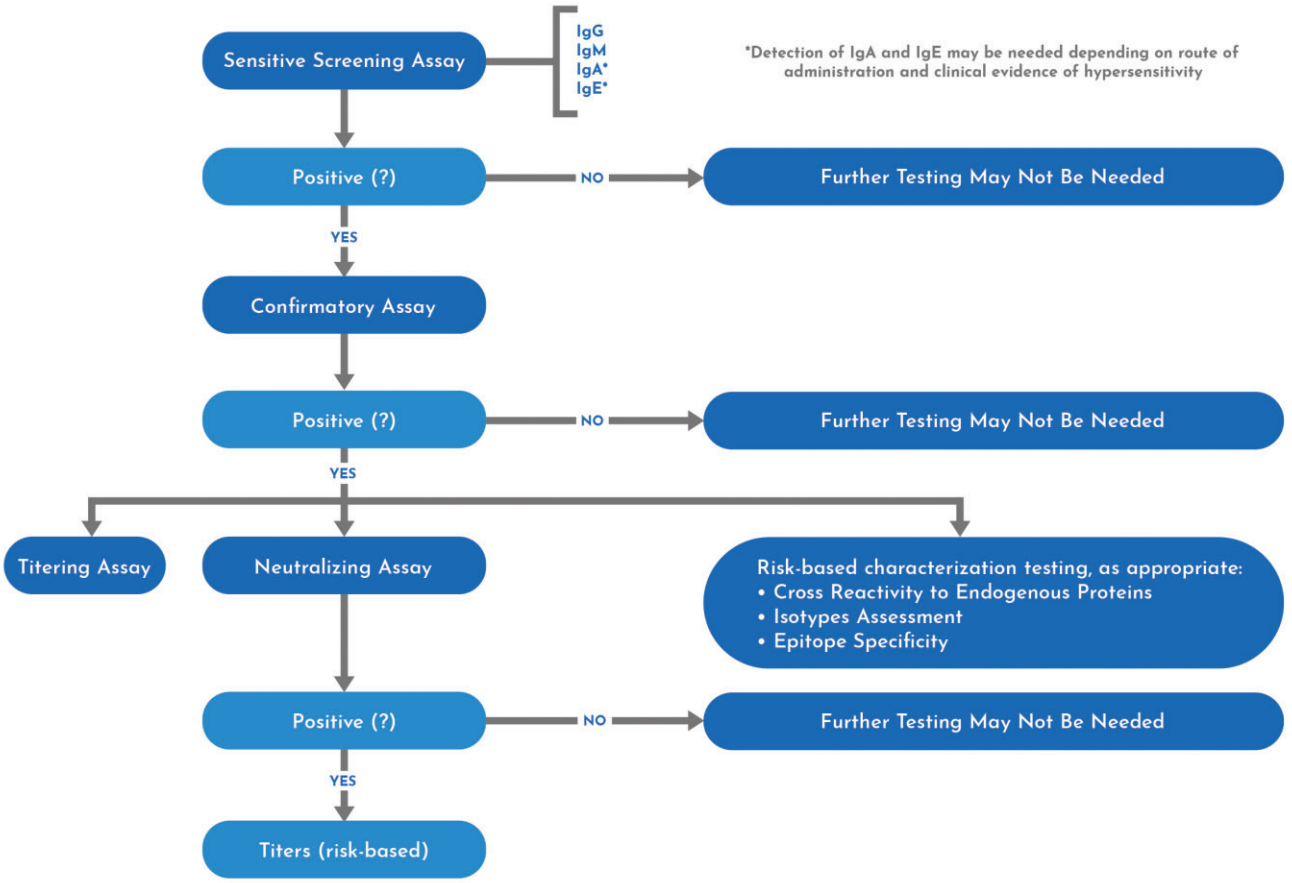
RISK ASSESSMENT UPDATES

In the 2019 guidance, the FDA revised its recommendations on immunogenicity risk assessment, stating that a risk assessment and a rationale for testing should be submitted in conjunction with the investigational new drug (IND) application. Previously, the FDA advised that sponsors should provide a rationale for immunogenicity testing rather than the risk assessment itself.

The risk assessment encompasses specific analyses and discussions on therapeutic protein factors that would influence its immunogenicity, including discussions on the drug product itself (eg, if it has an endogenous counterpart) and how likely a subject population is to respond to exposure to the therapeutic protein (eg, cancer patients who are often immune-compromised may mount a lower immune response to a protein, whereas people with autoimmune disorders would be more likely to develop immune responses).

In considering a risk assessment, sponsors should also examine the attributes of a product that may influence immunogenicity. Product-related factors that may contribute to immunogenicity include:

FIGURE 1



- Whether the product origin is human or foreign
- Novel structural formats, such as fusion proteins, bispecific antibodies, and other engineered antibodies
- Post-translational modifications
- The tendency of a therapeutic protein to aggregate
- Glycosylation or PEGylation
- The presence of impurities with adjuvant activity.

With respect to assay design, the FDA lays out a multi-tiered approach (Figure 1) for testing therapeutic proteins.[1] The approach consists of a sensitive screening assay for ADA followed by a confirmatory assay for any positive results. The FDA recommends that biologic drugs that cause a confirmed ADA assay result should undergo testing for neutralizing antibodies. Titer, isotype and domain specificity of the ADA may also be assessed along with PK, PD and clinical outcome evaluation.

STATISTICAL APPROACH TO DETERMINING CUT-POINT UPDATES

The cut-point of the assay determines whether the sample response is positive or negative; FDA suggests a cut-point having false-positive rate of approximately 5% is desirable for the initial screening assay because it maximizes detection of true positives, which is important for ensuring the adequate subjects who may develop antibodies to a therapeutic protein to be identified.

Historically, the assay cut-point was determined directly from a normal percentile, which assumes that distribution of results will follow a traditional bell-shaped curve. This method is simple, but it significantly underestimates the false positive rate, which results in a lower chance of satisfying the 5% false positive rate. For example, the traditional method for a screen assay is estimated to produce a cut-point only having less than 50% chance to satisfy the required 5% false positive rate.[2]

In the 2019 FDA guidance, the FDA requires sponsors to find a statistically sound method to determine the cut-point, whereas previous guidance documents stated that cut-point estimation could be achieved with a small number of samples. The 2019 guidance offers an approach wherein a screening assay should have at least 90% chance to satisfy the 5% false

positive rate, and a confirmatory assay should have at least 80% chance to satisfy the 1% false positive rate. The assay sensitivity can be calculated by interpolating the linear portion of the dilution curve to the assay cut-point. And low positive control, as an important system suitability control, should be set at a level that is consistently above the cut-point with a targeted 1% of failure rate. Statistical analysis can add value in determination of assay sensitivity and low positive control.

There is no generally accepted standard method for these statistical determinations. One way is a statistically sound estimation package, including outlier exclusion and cut-point estimation satisfying the new FDA requirements. The statistical methodology is based on order statistics, Bayesian, and Monte Carlo methods and can be applied to any assay data given that there are at least 50 samples. These methods are designed to satisfy or exceed the FDA confidence requirements without being too conservative. The required computations have been implemented using standard statistical programming languages SAS and R.

REMOVAL OF LONG-TERM STABILITY REQUIREMENT

Regarding sample stability, an important update in the 2019 guidance is that the expectation on long-term storage stability of positive control antibodies is now removed. Antibodies are known to be stable for at least two years when stored at -20°C or below, and evaluation of the positive control antibodies, which are essentially surrogate antibodies, for extended storage in deep freezers does not add value to the understanding of the ADA sample stability. The guidance now advises that sponsors minimize freeze-thaw cycles by appropriately aliquoting subjects' samples and evaluating short-term stability, including, as relevant, freeze-thaw cycle and refrigerator- and room-temperature stability of positive control antibodies. The agency, however, removed the wording on assessment of long-term stability.[1]

MINIMAL REQUIRED DILUTION

Matrix components, such as serum, saliva, or plasma, are known to interfere with assay selectivity, contributing to nonspecific signals and potentially obscuring positive results. Therefore, the FDA notes the frequent need to dilute subject samples to ensure the ability to detect ADA. The FDA 2019 guidance allows sponsors to use one of three definitions of the minimal required dilution – either the sample dilution that yields to highest signal-to-noise ratio, the sample dilution that results in a signal closest to assay diluent, or the sample dilution that results in the highest signal to variability ratio.[3] The expansion of definitions allows sponsors more options to better achieve optimal selectivity for an assay.

NEUTRALIZING ANTIBODIES

If immunogenicity testing finds and confirms positive ADAs, the FDA guides that sponsors should assess for NAbs. NAbs can have significant impact on drug PK, PD, safety, and efficacy, and the overall impact of antidrug antibodies may correlate with the activity of NAbs; however, designing appropriate assays for their detection is quite challenging as the traditional guide for developing the NAb strategy has been the risk of immunogenicity to patient safety.[5] The FDA has made extensive updates to its guidance for assays on neutralizing antibody action as the science has evolved.

One update is increased flexibility from the FDA for the format of assay that can be used to assess NAbs, and the guidance notes that selection of the assay format depends on various factors, such as the mechanism of action of the therapeutic and the selectivity, sensitivity, precision, and robustness of the assay.[1] The FDA explicitly allows employment of a highly sensitive PD marker or properly designed PK assay, or both, that generate data capable of informing clinical activity, in lieu of a NAb assay. NAb assays, especially cell-based assays, can be highly variable and with low sensitivity, as they are often executed in cell culture media and measure particular functional endpoints.[5] Therefore, hyper-variable cell-based NAb assays may not be as informative as a suitable PD or PK assay to indicate neutralizing antibody activities.

PRE-EXISTING ANTIBODIES

Frequently, humans may have antibodies to components of a therapeutic. For example, PEGylation is a common modification of certain proteins, which can reduce the immunogenicity of a protein, and prolong the circulatory life of a protein or improve water solubility of certain proteins. However, people can have pre-existing antibodies against it, given its frequent use in products, such as cosmetics. The fact

that people entering clinical trials may already have pre-existing antibodies challenges the statistical analysis traditionally used to differentiate between positive and negative assay results.

The challenge of pre-existing antibodies is to determine the cut-point that adequately differentiates negative ADA, pre-existing antibodies, and true ADA-positive samples and subsequent data reporting. The 2019 guidance provides more details on how to manage the statistical calculations on cut-point during method validation as well as discussing reporting strategies for capturing data around pre-existing antibodies. It gives clear definition of treatment-boosted ADAs, which refers to the situation in which there are pre-existing antibodies and the titer of antibodies increases after exposure to the therapeutic protein product.

DOCUMENTATION REQUIREMENTS

Prior to the 2019 guidance, immunogenicity data were dispersed throughout the electronic common technical document (eCTD), the standard format for submitting to the FDA, presenting challenges for reviewers to understand the big picture of a potential therapeutic protein's immunogenicity profile. The 2019 guidance provides detailed direction on documenting immunogenicity and requires an integrated immunogenicity summary report that gives a clear summary so FDA reviewers can understand the immunogenicity data up front. In addition, the FDA advises sponsors to arrange the integrated summary into distinct sections:[1]

- The Immunogenicity Risk Assessment should include "a concise immunogenicity risk assessment specific to the therapeutic protein product" as guided in FDA's Immunogenicity Assessment for Therapeutic Protein Products guidance.
- The Tiered Bioanalytical Strategy and Assay Validation Summaries section should summarize immunogenicity assessment strategies used during each phase of a clinical program and provide links to method development and validation reports for pivotal clinical studies.
- For the Clinical Study Design and Detailed Immunogenicity Sampling Plans section, FDA guides sponsors to provide the immunogenicity sampling plan for all clinical studies where immunogenicity assessments were performed as well as sampling time points for immunogenicity and PK of the therapeutic protein.
- The Clinical Immunogenicity Data Analysis section should provide a summary of immunogenicity analyses for all clinical studies with an immunogenicity component as well as detailed discussion on the impact that pre-existing or treatment-boosted or treatment-induced antibodies have on PK, PD, efficacy, and safety of the therapeutic protein product.
- For the Conclusions and Risk Evaluation and Mitigation Strategies (REMS) section, FDA requests how the candidate therapeutic protein affects the safety and efficacy of the product for the subject population. It should also show how immunogenicity will be monitored post-marketing and how it will be incorporated into any REMS. Finally, FDA requests a discussion around life cycle management of approved immunogenicity assays.

CONCLUSION

The 2019 FDA guidance on immunogenicity assessment intends to have the industry adopt a risk-based approach to fully understand the potential immunogenicity of the therapeutic proteins they are studying, thus to mitigate the impact of unwanted immune responses. The 2019 guidance adds clarity in method development, validation, and reporting processes. This article provides an understanding of the evolving immunogenicity assessment and current considerations for anti-drug antibody assay development. It should be pointed out that immunogenicity should not be evaluated in isolation. The treatment emergent antibodies should be assessed in conjunction with the structure of the therapeutic proteins, patient characteristics, and disease involved; and the impact of immunogenicity should be evaluated with pharmacokinetics, pharmacodynamics, sustainable of clinical response, safety, and efficacy of the protein therapeutics. These factors are interlinked and contribute to patients' immunogenicity profile. And because of these reasons, the FDA recommends providing an Integrated Summary Report of Immunogenicity in BLA submission that clearly defines the identification of risks, results for evaluation of all relevant risks and risk mitigation consideration.

SUMMARY

Immunogenicity assessment is one of the key elements in a biotherapeutic's development process. Each novel therapeutic protein and its assay system can have its unique product-specific challenges. With scientific and regulatory expertise, a seasoned bioanalytical partner can help biopharma companies ensure that the bioanalysis and immunogenicity assessment for their developmental drug meet evolving regulatory requirements, provide resolutions to the challenges, and empower your success. ◆

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BIOGRAPHIES

Leon Shi, PhD, Head of Biometrics, IMD, is the Biostatistician and head of Biometrics of IMD. His main duty includes preparing the Statistical Analysis Plan (SAP), reviewing trial protocol, creating summary tables/data listings/figures, sample size calculation, Standard Analysis, as well as, modeling and simulation. He holds a doctoral degree in Statistics from Oklahoma State University. He has accumulated over 15 years of experience in data analysis, SAS programming and mathematical modeling. During this period, he has participated in over 40+ Clinic trials with more than half of them including FDA Submission.

Lan Li is Vice President, Bioanalytical Services at WuXi AppTec Laboratory Testing Division. She has over 20 years of experience in the pharmaceutical industry in the United States, publishing numerous peer-reviewed articles in top scientific journals. Prior to joining WuXi AppTec, she worked for Alexion Pharmaceuticals, where she played critical roles in the discovery and development of Alexion's drug products, holding positions of the Head of Bioanalytical Development and the Leader of Research Strategy, and contributed significantly in marketing approval and label expansion of the biotherapeutics.

Dr. Jing Shi is Executive Director and Global Head of large molecule Bioanalysis of WuXi AppTec Laboratory Testing Division with extensive experience in global biotech/pharma and CRO industry. She joined WuXi AppTec in 2014 and is the head of China Immunochemistry Bioanalytical department, managing multisite operations. Her team provides bioanalytical method development, validation and sample testing services under GLP/GCP. Dr. Shi previously held leadership positions with AstraZenica and Sigma in the United States. She has extensive working experience at various drug development stages including cell line development, process development, toxicology, biologics drug substance/drug product characterization and preclinical/clinical bioanalytical analysis. In her most recent role with Sigma, she was the head of the Immunoassay laboratory, responsible for GMP lot release/stability testing and GLP bioanalytical testing using immunochemistry- or cell-based platforms. Dr. Shi obtained her B.S. in Cell Biology and Genetics from Peking University and Ph.D. in Cell Biology from University of Virginia.

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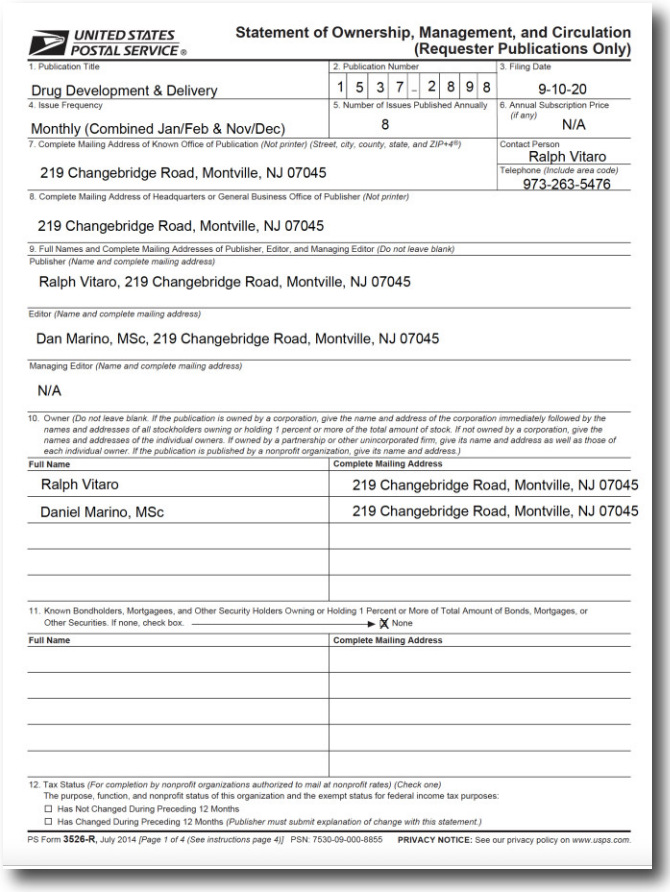

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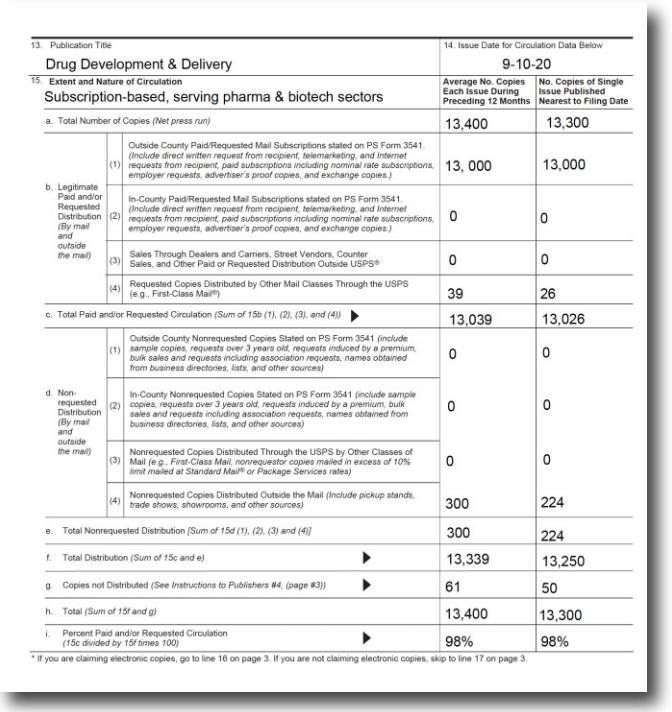

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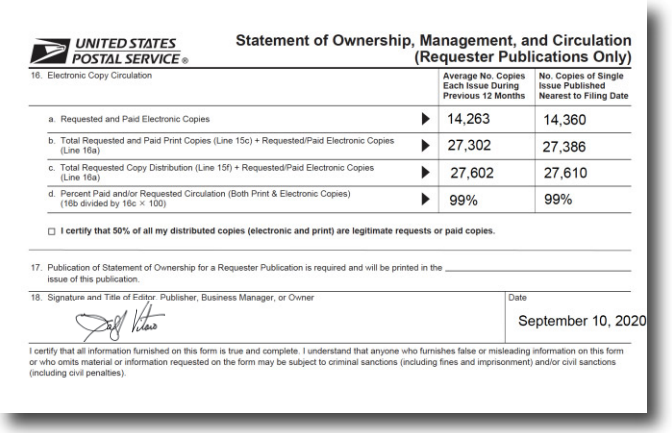

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